U.S. FOOD & DRUG ADMINISTRATION

September 18, 2017

Matthew Gee, M.Sc.
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511 Benedict Avenue
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Dear Mr. Gee:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of Siemens Healthcare Diagnostics Incorporated's ("Siemens Healthcare Diagnostics") ADVIA Centaur Zika test for the presumptive qualitative detection of Zika virus IgM antibodies in human serum and plasma (potassium EDTA or lithium heparin, each collected alongside a patient-matched serum specimen) specimens collected from individuals meeting the Centers for Disease Control and Prevention (CDC) Zika virus clinical criteria (e.g., clinical signs and symptoms associated 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), by laboratories in the United States (U.S.) that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high or moderate complexity tests, or by similarly qualified non-U.S. laboratories,[1] pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3). Specimens from symptomatic patients or returning travelers from endemic areas should not be collected prior to 8 days after onset of symptoms or risk of exposure, respectively. Where there are presumptive Zika positive results from the ADVIA Centaur Zika test, confirmation of the presence of anti-Zika IgM antibodies requires additional testing, as described in the Scope of Authorization of this letter (Section II) and in the authorized Instructions for Use document, and/or consideration alongside test results for other patient-matched specimens using the latest CDC testing algorithms for the diagnosis of Zika virus infection.[2]

On February 26, 2016, pursuant to section 564(b)(1)(C) of the Act (21 U.S.C. § 360bbb-3(b)(1)(C), the Secretary of Health and Human Services (HHS) determined that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that

[1] For ease of reference, this letter will refer to "laboratories in the United States (U.S.) that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high or moderate complexity tests, or by similarly qualified non-U.S. laboratories" as "authorized laboratories."
[2] Available at http://www.cdc.gov/zika/laboratories/lab-guidance.html (last updated on July 24, 2017).

involves Zika virus.[3] Pursuant to section 564(b)(1) of the Act (21 U.S.C. § 360bbb-3(b)(1)), and on the basis of such determination, the Secretary of HHS then declared that circumstances exist justifying the authorization of the emergency use of *in vitro* diagnostic tests for detection of Zika virus and/or diagnosis of Zika virus infection, subject to the terms of any authorization issued under 21 U.S.C. § 360bbb-3(a).[4]

Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act (21 U.S.C. § 360bbb-3(c)) are met, I am authorizing the emergency use of the ADVIA Centaur Zika test (as described in the Scope of Authorization section of this letter (Section II)) in individuals meeting CDC Zika virus clinical criteria (e.g., clinical signs and symptoms associated 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) (as described in the Scope of Authorization section of this letter (Section II)) for the presumptive qualitative detection of Zika virus infection by authorized laboratories, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the ADVIA Centaur Zika test for the presumptive qualitative detection of Zika virus IgM antibodies in the specified population meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

1. The Zika virus can cause Zika virus infection, a serious or life-threatening disease or condition to humans infected with the virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the ADVIA Centaur Zika test may be effective in diagnosing recent Zika virus infection, and that the known and potential benefits of the ADVIA Centaur Zika test for diagnosing Zika virus infection outweigh the known and potential risks of such product, when, for presumptive Zika positive results, additional testing (as described in the Instructions for Use document) is performed and/or test results for other patient-matched specimens (using the latest CDC testing algorithms for the diagnosis of Zika virus infection) are considered; and

3. There is no adequate, approved, and available alternative to the emergency use of the ADVIA Centaur Zika test for diagnosing Zika virus infection.[5]

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[3] As amended by the Pandemic and All-Hazards Preparedness Reauthorization Act, Pub. L. No. 113-5, under section 564(b)(1)(C) of the Act, the Secretary may make a determination of a public health emergency, or of a significant potential for a public health emergency.

[4] HHS. *Determination and Declaration Regarding Emergency Use of In Vitro Diagnostic Tests for Detection of Zika Virus and/or Diagnosis of Zika Virus Infection.* 81 Fed. Reg. 10878 (March 2, 2016).

[5] No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized ADVIA Centaur Zika test by authorized laboratories for the presumptive qualitative detection of Zika virus IgM antibodies in individuals meeting CDC Zika virus clinical criteria (e.g., clinical signs and symptoms associated 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) when, for presumptive Zika positive results, additional testing (as described in the Instructions for Use document) is performed[6] and/or test results for other patient-matched specimens (using the latest CDC testing algorithms for the diagnosis of Zika virus infection) are considered.

The Authorized ADVIA Centaur Zika Test

The ADVIA Centaur Zika test is an immunoassay for the *in vitro* presumptive qualitative detection of Zika virus IgM antibodies in human serum and potassium EDTA or lithium heparin plasma (each collected alongside a patient-matched serum specimen) specimens and other authorized specimen types from individuals meeting CDC Zika virus clinical criteria (e.g., clinical signs and symptoms associated 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).

The ADVIA Centaur Zika test is comprised of the ADVIA Centaur Zika Ab and ADVIA Centaur Zika IgM assays. All ADVIA Centaur Zika Ab reactive samples must be 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.

The ADVIA Centaur Zika test includes use of the ADVIA Centaur XP and/or ADVIA Centaur XPT immunoassay analyzers, and other authorized instruments.

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[6] As discussed in the Instructions for Use document, the additional testing for presumptive Zika IgM positive results is to be performed using the latest CDC testing algorithms for the diagnosis of Zika virus infection.

The ADVIA Centaur Zika test requires the following control materials and assay calibrators:

- ADVIA Centaur ZikaM low calibrator
- ADVIA Centaur ZikaM high calibrator
- ADVIA Centaur ZikaM Calibrator Assigned Value Card and barcode labels
- ADVIA Centaur ZikaM Master Curve Card
- ADVIA Centaur ZikaM Quality Control
  - 2 x 2 mL negative control
  - 2 x 2 mL positive control
  - Lot-specific assigned value card and barcode labels
- ADVIA Centaur ZikaAb Quality Control
  - 2 x 2 mL negative control
  - 2 x 2 mL positive control
  - Lot-specific assigned value card and barcode labels

Quality control requirements should be followed in conformance with local, state, and federal regulations or accreditation requirements and the user laboratory's standard quality control procedures.

The ADVIA Centaur Zika test also requires the use of additional materials and ancillary reagents commonly used in clinical laboratories and that are described in the authorized ADVIA Centaur Zika test Instructions for Use.

The above described ADVIA Centaur Zika test, when labeled consistently with the labeling authorized by FDA entitled "ADVIA Centaur Zika test" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), is authorized to be distributed to and used by authorized laboratories under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law. This labeling may be revised by Siemens Healthcare Diagnostics in consultation with, and with concurrence of, the Division of Microbiology Devices (DMD)/Office of In Vitro Diagnostics and Radiological Health (OIR)/Center for Devices and Radiological Health (CDRH).

The above described ADVIA Centaur Zika test is authorized to be accompanied by the following information pertaining to the emergency use, which is authorized to be made available to healthcare providers and patients:

- Fact Sheet for Healthcare Providers: Interpreting ADVIA Centaur Zika Test Results
- Fact Sheet for Patients: Understanding Results from the ADVIA Centaur Zika Test

Other Fact Sheets developed by Siemens Healthcare Diagnostics in consultation with, and with concurrence of, the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC) and DMD/OIR/CDRH may be authorized to accompany the above described ADVIA Centaur Zika test and to be made available to healthcare providers and patients.

As described in Section IV below, Siemens Healthcare Diagnostics is also authorized to make available additional information relating to the emergency use of the authorized ADVIA Centaur Zika test that is consistent with, and does not exceed, the terms of this letter of authorization.

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the authorized ADVIA Centaur Zika test in the specified population, when used for presumptive qualitative detection of Zika virus IgM antibodies and used consistently with the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of such a product.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the authorized ADVIA Centaur Zika test may be effective in the diagnosis of recent Zika virus infection, when used consistently with the Scope of Authorization of this letter (Section II), pursuant to section 564(c)(2)(A) of the Act.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, and concludes that the authorized ADVIA Centaur Zika test, when used to diagnose Zika virus infection in the specified population (as described in the Scope of Authorization of this letter (Section II)), meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized ADVIA Centaur Zika test under this EUA must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section IV). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the ADVIA Centaur Zika test described above is authorized to diagnose Zika virus infection in individuals meeting CDC Zika virus clinical criteria (e.g., clinical signs and symptoms associated 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).

This EUA will cease to be effective when the HHS declaration that circumstances exist to justify the EUA is terminated under section 564(b)(2) of the Act or when the EUA is revoked under section 564(g) of the Act.

III. Waiver of Certain Requirements

I am waiving the following requirements for the ADVIA Centaur Zika test during the duration of this EUA:

- Current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the ADVIA Centaur Zika test.

- Labeling requirements for cleared, approved, or investigational devices, including labeling requirements under 21 CFR 809.10 and 21 CFR 809.30, except for the intended use statement (21 CFR 809.10(a)(2), (b)(2)); adequate directions for use (21 U.S.C. 352(f)), (21 CFR 809.10(b)(5), (7), and (8)); any appropriate limitations on the use of the device including information required under 21 CFR 809.10(a)(4); and any available information regarding performance of the device, including requirements under 21 CFR 809.10(b)(12).

IV. Conditions of Authorization

Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

Siemens Healthcare Diagnostics and Its Authorized Distributor(s)

A. Siemens Healthcare Diagnostics and its authorized distributor(s) will distribute the authorized ADVIA Centaur Zika test with the authorized labeling only to authorized laboratories. Siemens Healthcare Diagnostics may request changes to the authorized labeling. Such requests will be made by Siemens Healthcare Diagnostics in consultation with, and require concurrence of, DMD/OIR/CDRH.

B. Siemens Healthcare Diagnostics and its authorized distributor(s) will provide to authorized laboratories the authorized ADVIA Centaur Zika test Fact Sheet for Healthcare Providers and the authorized ADVIA Centaur Zika test Fact Sheet for Patients, and any additional ADVIA Centaur Zika test Fact Sheets for Healthcare Providers and Patients that OCET/OCS/OC and DMD/OIR/CDRH may authorize.

C. Siemens Healthcare Diagnostics and its authorized distributor(s) will make available on their websites the authorized ADVIA Centaur Zika test Fact Sheet for Healthcare Providers and the authorized ADVIA Centaur Zika test Fact Sheet for Patients, and any additional ADVIA Centaur Zika test Fact Sheets for Healthcare Providers and Patients that OCET/OCS/OC and DMD/OIR/CDRH may authorize.

D. Siemens Healthcare Diagnostics and its authorized distributor(s) will inform authorized laboratories and relevant public health authority(ies) of this EUA, including the terms and conditions herein.

E. Siemens Healthcare Diagnostics and its authorized distributor(s) will ensure that authorized laboratories using the authorized ADVIA Centaur Zika test have a process in place for reporting test results to healthcare providers and relevant public health authorities, as appropriate.[7]

F. Through a process of inventory control, Siemens Healthcare Diagnostics and its authorized distributor(s) will maintain records of device usage.

G. Siemens Healthcare Diagnostics and its authorized distributor(s) will collect information on the performance of the test. Siemens Healthcare Diagnostics will report to FDA any suspected occurrence of false positive and false negative results and significant deviations from the established performance characteristics of the test of which Siemens Healthcare Diagnostics becomes aware.

H. Siemens Healthcare Diagnostics and its authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized ADVIA Centaur Zika test that is consistent with, and does not exceed, the terms of this letter of authorization.

Siemens Healthcare Diagnostics

I. Siemens Healthcare Diagnostics will notify FDA of any authorized distributor(s) of the ADVIA Centaur Zika test, including the name, address, and phone number of any authorized distributor(s).

J. Siemens Healthcare Diagnostics will provide its authorized distributor(s) with a copy of this EUA, and communicate to its authorized distributor(s) any subsequent amendments that might be made to this EUA and its authorized accompanying materials (e.g., Fact Sheets, Instructions for Use).

K. Siemens Healthcare Diagnostics may request changes to the authorized ADVIA Centaur Zika test Fact Sheet for Healthcare Providers and the authorized ADVIA Centaur Zika test Fact Sheet for Patients. Siemens Healthcare Diagnostics may also develop new ADVIA Centaur Zika test Fact Sheets for Healthcare Providers and Patients, if appropriate, and may request changes to such Fact Sheets. All such requests listed in this condition of authorization will be made by Siemens Healthcare Diagnostics in consultation with, and require concurrence of, OCET/OCS/OC and DMD/OIR/CDRH.

L. Siemens Healthcare Diagnostics may request the addition of other instruments for use with the authorized ADVIA Centaur Zika test. Such requests will be made by Siemens Healthcare Diagnostics in consultation with, and require concurrence of, DMD/OIR/CDRH.

[7] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that Siemens Healthcare Diagnostics and authorized laboratories consult with the applicable country, state, or territory health department(s). According to CDC, Zika is a nationally notifiable condition (see http://www.cdc.gov/zika/).

M. Siemens Healthcare Diagnostics may request the addition of other ancillary reagents for use with the authorized ADVIA Centaur Zika test. Such requests will be made by Siemens Healthcare Diagnostics in consultation with, and require concurrence of, DMD/OIR/CDRH.

N. Siemens Healthcare Diagnostics may request the addition of other specimen types for use with the authorized ADVIA Centaur Zika test. Such requests will be made by Siemens Healthcare Diagnostics in consultation with, and require concurrence of, DMD/OIR/CDRH.

O. Siemens Healthcare Diagnostics may request the addition of other control materials for use with the authorized ADVIA Centaur Zika test. Such requests will be made by Siemens Healthcare Diagnostics in consultation with, and require concurrence of, DMD/OIR/CDRH.

P. Siemens Healthcare Diagnostics may request substitution for or changes to the authorized materials used in the detection process of the human anti-Zika IgM in the specimen. Such requests will be made by Siemens Healthcare Diagnostics in consultation with, and require concurrence of, DMD/OIR/CDRH.

Q. Siemens Healthcare Diagnostics will track adverse events and report to FDA under 21 CFR Part 803.

R. Siemens Healthcare Diagnostics will evaluate the performance of the ADVIA Centaur Zika test with any FDA-recommended or established panel(s) of characterized clinical specimens, and will submit that performance data to FDA. After DMD/OIR/CDRH's review of and concurrence with the data, Siemens Healthcare Diagnostics will update its labeling, in consultation with, and with concurrence of, DMD/OIR/CDRH, to reflect the additional testing.

S. Siemens Healthcare Diagnostics will assess traceability[8] of the ADVIA Centaur Zika test with any FDA-recommended reference material(s). After submission to FDA and DMD/OIR/CDRH's review of and concurrence with the data, Siemens Healthcare Diagnostics will update its labeling to reflect the additional testing.

T. Siemens Healthcare Diagnostics will track the performance of the ADVIA Centaur Zika test and report to DMD/OIR/CDRH on a semi-annual basis.

[8] Traceability refers to tracing analytical sensitivity/reactivity back to a FDA-recommended reference material.

Authorized Laboratories

U. Authorized laboratories will include with reports of the results of the ADVIA Centaur Zika test the authorized Fact Sheet for Healthcare Providers and the authorized Fact Sheet for Patients, and any additional ADVIA Centaur Zika test Fact Sheets for Healthcare Providers and Patients that OCET/OCS/OC and DMD/OIR/CDRH may authorize. Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.

V. Authorized laboratories will perform the ADVIA Centaur Zika test on only human serum or plasma (potassium EDTA or lithium heparin, each collected alongside a patient-matched serum specimen) specimens or with other authorized specimen types.

W. If non-serum specimens are used with the ADVIA Centaur Zika test, authorized laboratories responsible for collecting the patient specimen must collect a patient-matched serum specimen, or if this is not possible, an additional serum specimen must be collected soon after the original specimen. This is to facilitate any additional testing that may be required, using the latest CDC testing algorithms for the diagnosis of Zika virus infection, to confirm Zika virus infection.

X. Authorized laboratories must read the results of the ADVIA Centaur Zika test on the ADVIA Centaur XP, ADVIA Centaur XPT, or on other authorized instruments.

Y. Within the United States and its territories, authorized laboratories will report all Presumptive Zika Positive results to Siemens Healthcare Diagnostics.

Z. Authorized laboratories will report only the final interpretation of algorithm test results (Presumptive Zika Positive, Negative for IgM antibodies to Zika virus, or Negative for antibodies to Zika virus), as described in the Instructions for Use document, to healthcare providers.

AA. Authorized laboratories will have a process in place to assure that, for Presumptive Zika Positive results, additional testing (as described in the Instructions for Use document) is performed and/or test results for other patient-matched specimens, using the latest CDC testing algorithms for the diagnosis of Zika virus infection, are considered.

BB. Authorized laboratories will have a process in place for reporting test results to healthcare providers and relevant public health authorities, as appropriate.[9]

[9] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that Siemens Healthcare Diagnostics and authorized laboratories consult with the applicable country, state, or territory health department(s). According to CDC, Zika is a nationally notifiable condition (see http://www.cdc.gov/zika/).

CC. Authorized laboratories will collect information on the performance of the ADVIA Centaur Zika test and report to DMD/OIR/CDRH (*via* email CDRH-EUA-Reporting@fda.hhs.gov) and Siemens Healthcare Diagnostics any suspected occurrence of false negative and false positive results and significant deviations from the established performance characteristics of which they become aware.

DD. All laboratory personnel using the assay must be appropriately trained in performing and interpreting immunoassay techniques, use appropriate laboratory and personal protective equipment when handling this kit, and use the test in accordance with the authorized labeling. All laboratory personnel using the assay must also be trained in and be familiar with the interpretation of results of the ADVIA Centaur Zika test.

Siemens Healthcare Diagnostics, Its Authorized Distributor(s), and Authorized Laboratories

EE. Siemens Healthcare Diagnostics, its authorized distributor(s), and authorized laboratories will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to FDA for inspection upon request.

Conditions Related to Advertising and Promotion

FF. All advertising and promotional descriptive printed matter relating to the use of the authorized ADVIA Centaur Zika test shall be consistent with the authorized Fact Sheets and authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

GG. All advertising and promotional descriptive printed matter relating to the use of the authorized ADVIA Centaur Zika test shall clearly and conspicuously state that:

- This test has not been FDA cleared or approved;
- This test has been authorized by FDA under an EUA for use by authorized laboratories;
- This test has been authorized only for the diagnosis of Zika virus infection and not for any other viruses or pathogens; and
- This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of *in vitro* diagnostic tests for detection of Zika virus and/or diagnosis of Zika virus infection under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

No advertising or promotional descriptive printed matter relating to the use of the authorized ADVIA Centaur Zika test may represent or suggest that this test is safe or effective for the diagnosis of Zika virus infection.

The emergency use of the authorized ADVIA Centaur Zika test as described in this letter of authorization must comply with the conditions and all other terms of this authorization.

V. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of *in vitro* diagnostic tests for detection of Zika virus and/or diagnosis of Zika virus infection is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Sincerely,

Rachel Sherman, M.D., M.P.H.
Principal Deputy Commissioner

Enclosures