DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

July 29, 2016

Ingrid Mehlhorn
Regulatory Affairs
Siemens Healthcare Diagnostics Inc.
725 Potter St.
Berkeley, CA 94710

Dear Dr. Mehlhorn:

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 Inc.'s ("Siemens") VERSANT® Zika RNA 1.0 Assay (kPCR) Kit for the qualitative detection of RNA from Zika virus in human serum, EDTA plasma, and urine (collected alongside a patient-matched serum or plasma specimen) from individuals meeting 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 epidemiologic 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 complexity tests, or by similarly qualified non-U.S. laboratories, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3).[1] Assay results are for the identification of Zika virus RNA. Zika virus RNA is generally detectable in these specimens during the acute phase of infection (approximately 7 days in serum, possibly longer in urine, following onset of symptoms, if present). Positive results are indicative of current infection.

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 involves Zika virus.[2] 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

[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 complexity tests, or by similarly qualified non-U.S. laboratories" as "authorized laboratories."

[2] 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.

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).[3]

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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit (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 epidemiologic criteria for which Zika virus testing may be indicated) (as described in the Scope of Authorization section of this letter (Section II)) for the 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit for the detection of Zika virus and diagnosis of Zika virus infection 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit, when used with the specified instrument and in accordance with the Scope of Authorization, may be effective in detecting Zika virus and diagnosing Zika virus infection, and that the known and potential benefits of the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit for detecting Zika virus and diagnosing Zika virus infection outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit for detecting Zika virus and diagnosing Zika virus infection.[4]

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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit by authorized laboratories for the detection of RNA from Zika virus and diagnosis of 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.,

[3] 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).

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

history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiologic criteria for which Zika virus testing may be indicated).

The Authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit

The VERSANT® Zika RNA 1.0 Assay (kPCR) Kit is a real-time PCR (RT-PCR) assay for the qualitative detection of RNA from Zika virus in serum, EDTA plasma, and urine (collected alongside a patient-matched serum or plasma specimen) and other authorized specimen types.

To perform the VERSANT® Zika RNA 1.0 Assay (kPCR), samples are first extracted to isolate the Zika virus RNA. Nucleic acids are isolated and purified from the sample using either the Siemens' automated VERSANT® kPCR Sample Preparation (SP) system (also referred to as VERSANT® kPCR Molecular System SP) with the VERSANT® MiPLX Software Solution and the VERSANT® Sample Preparation 1.0 Reagents or with the QIAamp viral RNA Mini Kit with manual extraction, or with other authorized extraction methods. An Internal Control sequence is added to the sample prior to extraction and is used as a control for the sample extraction and the amplification reaction.

Purified RNA is then added to a PCR plate containing Zika Enzyme Mix and Zika Primer/Probe Mix, and the wells are sealed. The purified nucleic acids are first reverse transcribed into cDNAs. In the process, the probes anneal to the specific target sequences located between the respective forward and reverse primers. The assay targets two regions of the Zika virus genome. The dual-labeled probes include fluorescent dyes and quenchers and specifically detect the presence of Zika virus and Internal Control amplicons during amplification. During the extension phase of the PCR cycle, the 5' nuclease activity of Taq polymerase degrades the probes, causing the reporter dyes to separate from the quencher dyes, generating fluorescent signals. With each cycle, additional reporter dye molecules are cleaved from their respective probes, increasing the fluorescence intensity.

The RT-PCR is performed on the QuantStudio™ 5 Real-Time PCR System (Thermo Fisher Scientific), the CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad), the Applied Biosystems® 7500 Fast Dx Real-Time PCR Instrument (Thermo Fisher Scientific) or other authorized instruments.

The VERSANT® Zika RNA 1.0 Assay (kPCR) Kit includes the following materials, or other authorized materials or ancillary products:

- Zika Enzyme Mix
- Zika Primer/Probe Mix
- Zika Internal Control
- Zika Negative Control
- Zika Positive Control
- Water (nuclease free)

The VERSANT® Zika RNA 1.0 Assay (kPCR) Kit requires the following control materials, or other authorized control materials, to be included in each run; all assay controls listed below must generate expected results in order for a test to be considered valid:

- VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Internal Control

  - The internal control consists of a non-Zika virus RNA that is added and co-purified with each specimen, Positive Control, and Negative Control, and that is amplified by a specific primers and probe set.
  - The internal control RNA controls for sample extraction, reverse transcription, amplification and detection, and also ensures the absence of non-specific PCR inhibition of a sample.

- VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Negative Control
  - PCR grade water.
  - A negative control should be included in each run of specimen extractions to monitor Zika virus contamination.

- VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Positive Control
  - Inactivated Cultured Zika Virus Strain MR766.
  - A positive control is included in each run of specimen extractions to monitor nucleic acid isolation and detection of Zika virus RNA.

To produce a valid run, the test controls must meet the performance specifications outlined in the Instructions for Use.

The above described VERSANT® Zika RNA 1.0 Assay (kPCR) Kit, when labeled consistently with the labeling authorized by FDA entitled "VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Instructions for Use" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), which may be revised by Siemens in consultation with the Division of Microbiology Devices (DMD)/Office of In Vitro Diagnostics and Radiological Health (OIR)/Center for Devices and Radiological Health (CDRH), 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.

The above described VERSANT® Zika RNA 1.0 Assay (kPCR) Kit is authorized to be accompanied by the following information pertaining to the emergency use, which is authorized to be made available to health care providers, pregnant women, and other patients:

- Fact Sheet for Health Care Providers: Interpreting VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Test Results
- Fact Sheet for Pregnant Women: Understanding Results from the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit
- Fact Sheet for Patients: Understanding Results from the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit

As described in Section IV below, Siemens is also authorized to make available additional information relating to the emergency use of the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit in the specified population, when used for detection of Zika virus and to diagnose Zika virus infection 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit may be effective in the detection of Zika virus and diagnosis of 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit, when used for detection of Zika virus and 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit described above is authorized to detect Zika virus and 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 geographic regions during a period of active Zika virus transmissions at the time of travel, or other epidemiologic 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit.

- 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 Inc. and Its Authorized Distributor(s)

A. Siemens and its authorized distributor(s) will distribute the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit with the authorized labeling, as may be revised by Siemens in consultation with DMD/OIR/CDRH, only to authorized laboratories.

B. Siemens and its authorized distributor(s) will provide to authorized laboratories the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Fact Sheet for Health Care Providers, the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Fact Sheet for Pregnant Women, and the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Fact Sheet for Patients.

C. Siemens and its authorized distributor(s) will make available on their websites the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Fact Sheet for Health Care Providers, the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Fact Sheet for Pregnant Women, and the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Fact Sheet for Patients.

D. Siemens 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 and its authorized distributor(s) will ensure that authorized laboratories using the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit have a process in place for reporting test results to health care providers and relevant public health authorities, as appropriate.[5]

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

G. Siemens and its authorized distributor(s) will collect information on the performance of the test. Siemens 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 becomes aware.

H. Siemens and its authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit that is consistent with, and does not exceed, the terms of this letter of authorization.

[5] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that Siemens 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/).

Siemens Healthcare Diagnostics Inc.

I. Siemens will notify FDA of any authorized distributor(s) of the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit, including the name, address, and phone number of any authorized distributor(s).

J. Siemens 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 may request changes to the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Fact Sheet for Health Care Providers, the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Fact Sheet for Pregnant Women, and the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit Fact Sheet for Patients. Such requests will be made by Siemens in consultation with, and require concurrence of, DMD/OIR/CDRH.

L. Siemens may request the addition of other instruments for use with the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit. Such requests will be made by Siemens in consultation with, and require concurrence of, DMD/OIR/CDRH.

M. Siemens may request the addition of other extraction methods for use with the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit. Such requests will be made by Siemens in consultation with, and require concurrence of, DMD/OIR/CDRH.

N. Siemens may request the addition of other specimen types for use with the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit. Such requests will be made by Siemens in consultation with, and require concurrence of, DMD/OIR/CDRH.

O. Siemens may request the addition of other control materials for use with the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit. Such requests will be made by Siemens in consultation with, and require concurrence of, DMD/OIR/CDRH.

P. Siemens may request the addition of other materials and ancillary reagents for use with the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit. Such requests will be made by Siemens in consultation with, and require concurrence of, DMD/OIR/CDRH.

Q. Siemens will assess traceability[6] of the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit with FDA-recommended reference material(s). After submission to FDA and DMD/OIR/CDRH's review of and concurrence with the data, Siemens will update its labeling to reflect the additional testing.

R. Siemens will track adverse events and report to FDA under 21 CFR Part 803.

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

Authorized Laboratories

S. Authorized laboratories will include with reports of the results of the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit the authorized Fact Sheet for Health Care Providers, the authorized Fact Sheet for Pregnant Women, and the authorized Fact Sheet for Patients. Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.

T. Authorized laboratories will perform the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit on the QuantStudio™ 5 Real-Time PCR System, the CFX96 Touch™ Real-Time PCR Detection System, the Applied Biosystems® 7500 Fast Dx Real-Time PCR Instrument or other authorized instruments.

U. Authorized laboratories will perform the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit using either the VERSANT® kPCR Sample Preparation (SP) system (also referred to as VERSANT® kPCR Molecular System SP) with the VERSANT® MiPLX Software Solution and the VERSANT® Sample Preparation 1.0 Reagents or with the QIAamp viral RNA Mini Kit with manual extraction, or with other authorized extraction methods.

V. Authorized laboratories will perform the VERSANT® Zika RNA 1.0 Assay (kPCR) Kit on serum, EDTA plasma, or urine (collected alongside a patient-matched serum or plasma specimen) or with other authorized specimen types.

W. Authorized laboratories will have a process in place for reporting test results to health care providers and relevant public health authorities, as appropriate.[7]

X. Authorized laboratories will collect information on the performance of the test and report to Siemens, any suspected occurrence of false positive or false negative results of which they become aware.

Y. All laboratory personnel using the test should be appropriately trained in RT-PCR techniques and use appropriate laboratory and personal protective equipment when handling this kit, and use the test in accordance with the authorized labeling.

Siemens Healthcare Diagnostics Inc., its Authorized Distributor(s) and Authorized Laboratories

Z. Siemens, 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

AA. All advertising and promotional descriptive printed matter relating to the use of the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit shall be consistent with the

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

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.

BB. All advertising and promotional descriptive printed matter relating to the use of the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit 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 detection of RNA from Zika virus and diagnosis of Zika virus infection, 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 VERSANT® Zika RNA 1.0 Assay (kPCR) Kit may represent or suggest that this test is safe or effective for the diagnosis of Zika virus infection.

The emergency use of the authorized VERSANT® Zika RNA 1.0 Assay (kPCR) Kit 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,

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Luciana Borio, M.D.
Acting Chief Scientist
Food and Drug Administration

Enclosures