DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

May 13, 2016

Dr. Sven Cramer
Director, Regulatory Affairs
altona Diagnostics GmbH
Mörkenstraβe 12
22767 Hamburg
Germany

Dear Dr. Cramer:

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 altona Diagnostics GmbH's RealStar® Zika Virus RT-PCR Kit U.S. for the qualitative detection of RNA from Zika virus in human serum and urine (collected alongside a patient-matched serum specimen) specimens 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 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 viral RNA. Zika viral RNA is generally detectable in serum during the acute phase of infection (approximately 7 days 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 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 RealStar® Zika Virus RT-PCR Kit U.S. (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 RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S., 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 RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S. 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., 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).

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[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.

The Authorized RealStar® Zika Virus RT-PCR Kit U.S.

altona Diagnostics GmbH's RealStar® Zika Virus RT-PCR Kit U.S. is a real-time reverse transcriptase PCR (rRT-PCR) for the *in vitro* qualitative detection of Zika virus RNA in serum and urine (collected alongside a patient-matched serum specimen) specimens collected 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 epidemiologic criteria for which Zika virus testing may be indicated). The RealStar® Zika Virus RT-PCR Kit U.S. can also be used with other authorized specimen types. The test procedure consists of nucleic acid extraction using the Qiagen QIAamp® Viral RNA Mini kit, or other authorized extraction method, followed by rRT-PCR on the ABI Prism® 7500 SDS instrument, the ABI Prism® 7500 Fast SDS instrument, the LightCycler® 480 Instrument II, the CFX96™ Real-Time PCR Detection System, the CFX96™ Deep Well Real-Time PCR Detection System, the Rotor-Gene® 6000 instrument, the Rotor-Gene® Q 5/6 plex/MDx Platform or other authorized instruments.

The RealStar® Zika Virus RT-PCR Kit U.S. includes a primer and dual-labeled hydrolysis (Taqman®) probe set targeting a nucleotide sequence within the Zika virus genome to be used in the *in vitro* qualitative detection of Zika virus RNA isolated from human serum, urine and any other authorized specimens. 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. During the extension phase of the PCR cycle, the 5' nuclease activity of Taq polymerase degrades the probe, causing the reporter dye to separate from the quencher dye, generating fluorescent signals. With each cycle, additional reporter dye molecules are cleaved from their respective probes, increasing the fluorescence intensity.

The RealStar® Zika Virus RT-PCR Kit U.S. includes the following materials:

- RealStar® Zika Virus RT-PCR Kit U.S. Primer and Probe sets for the detection of Zika virus and the Internal Control
    - Master A
    - Master B

The RealStar® Zika Virus RT-PCR Kit U.S. requires the following control materials; all assay controls listed below should be run concurrently with all test samples and must generate expected results in order for a test to be considered valid:

- RealStar® Zika Virus RT-PCR Kit U.S. Negative Control
    - PCR grade water
    - A negative control is included in each batch of specimen extractions to monitor Zika virus contamination

- RealStar® Zika Virus RT-PCR Kit U.S. Positive Control
    - Zika virus strain *in vitro* transcript which contains the target sequence used by the RealStar® Zika Virus RT-PCR Kit U.S.
    - A positive control is included in each batch of specimen extractions to

monitor nucleic acid isolation and detection of Zika virus RNA

- RealStar® Zika Virus RT-PCR Kit U.S. Internal Control
  - RNA target included in each specimen, Positive Control, and Negative Control
  - Consists of an artificial RNA molecule with no homologies to any other known sequences, added to the nucleic acid extraction procedure
  - Ensures the absence of non-specific PCR inhibition of a sample

The above described RealStar® Zika Virus RT-PCR Kit U.S., when labeled consistently with the labeling authorized by FDA entitled "RealStar® Zika Virus RT-PCR Kit U.S. Instructions for Use" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), which may be revised by altona Diagnostics GmbH in consultation with FDA, 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 RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S. Test Results
- Fact Sheet for Pregnant Women: Understanding Results from the RealStar® Zika Virus RT-PCR Kit U.S.
- Fact Sheet for Patients: Understanding Results from the RealStar® Zika Virus RT-PCR Kit U.S.

As described in Section IV below, altona Diagnostics GmbH is also authorized to make available additional information relating to the emergency use of the authorized RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S., 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 RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S. 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 RealStar® Zika Virus RT-PCR Kit U.S.

- 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:

altona Diagnostics GmbH and Its Authorized Distributor(s)

A. altona Diagnostics GmbH and its authorized distributor(s) will distribute the authorized RealStar® Zika Virus RT-PCR Kit U.S. with the authorized labeling, as may be revised by altona Diagnostics GmbH in consultation with FDA, only to authorized laboratories.

B. altona Diagnostics GmbH and its authorized distributor(s) will provide to authorized laboratories the authorized RealStar® Zika Virus RT-PCR Kit U.S. Fact Sheet for Health Care Providers, the authorized RealStar® Zika Virus RT-PCR Kit U.S. Fact Sheet for Pregnant Women, and the authorized RealStar® Zika Virus RT-PCR Kit U.S. Fact Sheet for Patients.

C. altona Diagnostics GmbH and its authorized distributor(s) will make available on their websites the authorized RealStar® Zika Virus RT-PCR Kit U.S. Fact Sheet for Health Care Providers, the authorized RealStar® Zika Virus RT-PCR Kit U.S. Fact Sheet for Pregnant Women, and the authorized RealStar® Zika Virus RT-PCR Kit U.S. Fact Sheet for Patients.

D. altona Diagnostics GmbH 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. altona Diagnostics GmbH and its authorized distributor(s) will ensure that authorized laboratories using the authorized RealStar® Zika Virus RT-PCR Kit U.S. 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, altona Diagnostics GmbH and its authorized distributor(s) will maintain records of device usage.

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

H. altona Diagnostics GmbH and its authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized RealStar® Zika Virus RT-PCR Kit U.S. that is consistent with, and does not exceed, the terms of this letter of authorization.

altona Diagnostics GmbH

I. altona Diagnostics GmbH will notify FDA of any authorized distributor(s) of the RealStar® Zika Virus RT-PCR Kit U.S., including the name, address, and phone number of any authorized distributor(s).

J. altona Diagnostics GmbH 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

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

sheets, instructions for use).

K. altona Diagnostics GmbH may request changes to the authorized RealStar® Zika Virus RT-PCR Kit U.S. Fact Sheet for Health Care Providers, the authorized RealStar® Zika Virus RT-PCR Kit U.S. Fact Sheet for Pregnant Women, and the authorized RealStar® Zika Virus RT-PCR Kit U.S. Fact Sheet for Patients. Such requests will be made by altona Diagnostics GmbH in consultation with, and require concurrence of, FDA.

L. altona Diagnostics GmbH may request the addition of other real-time PCR instruments for use with the authorized RealStar® Zika Virus RT-PCR Kit U.S. Such requests will be made by altona Diagnostics GmbH in consultation with, and require concurrence of, FDA.

M. altona Diagnostics GmbH may request the addition of other extraction methods for use with the authorized RealStar® Zika Virus RT-PCR Kit U.S. Such requests will be made by altona Diagnostics GmbH in consultation with, and require concurrence of, FDA.

N. altona Diagnostics GmbH may request the addition of other specimen types for use with the authorized RealStar® Zika Virus RT-PCR Kit U.S. Such requests will be made by altona Diagnostics GmbH in consultation with, and require concurrence of, FDA.

O. altona Diagnostics GmbH will assess traceability[6] of the RealStar® Zika Virus RT-PCR Kit U.S. with a FDA-recommended reference material. After submission to FDA and FDA's review of and concurrence with the data, altona Diagnostics GmbH will update its labeling to reflect the additional testing.

P. altona Diagnostics GmbH will track adverse events and report to FDA under 21 CFR Part 803.

Authorized Laboratories

Q. Authorized laboratories will include with reports of the results of the RealStar® Zika Virus RT-PCR Kit U.S. 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.

R. Authorized laboratories will perform the RealStar® Zika Virus RT-PCR Kit U.S. on the ABI Prism® 7500 SDS instrument, the ABI Prism® 7500 Fast SDS instrument, the LightCycler® 480 Instrument II, the CFX96™ Real-Time PCR Detection System, the CFX96™ Deep Well Real-Time PCR Detection System, the Rotor-Gene® 6000 instrument, the Rotor-Gene® Q 5/6 plex/MDx Platform or other authorized instruments.

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

[6] Traceability refers to tracing analytical sensitivity/reactivity back to a FDA recommended reference material.
[7] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that altona Diagnostics GmbH and authorized laboratories consult with the applicable state or territory health department(s). According to CDC, Zika is a nationally notifiable condition. http://www.cdc.gov/zika/.

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

U. 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.

altona Diagnostics GmbH, Its Authorized Distributor(s) and Authorized Laboratories

V. altona Diagnostics GmbH, 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

W. All advertising and promotional descriptive printed matter relating to the use of the authorized RealStar® Zika Virus RT-PCR Kit U.S. shall be consistent with the 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.

X. All advertising and promotional descriptive printed matter relating to the use of the authorized RealStar® Zika Virus RT-PCR Kit U.S. 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, 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 RealStar® Zika Virus RT-PCR Kit U.S. may represent or suggest that this test is safe or effective for the diagnosis of Zika virus infection.

The emergency use of the authorized RealStar® Zika Virus RT-PCR Kit U.S. 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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Robert M. Califf, M.D.
Commissioner of Food and Drugs

Enclosures