DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

July 19, 2016

Michael Seymour
Manager of Regulatory Affairs and Quality Assurance
Viracor-IBT Laboratories, Inc.
1001 NW Technology Drive
Lee's Summit, MO 64086

Dear Mr. Seymour:

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 Viracor-IBT Laboratories, Inc.'s ("Viracor-IBT") Zika Virus Real-time RT-PCR test for the qualitative detection of RNA from Zika virus in human serum, plasma or 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). Testing is limited to Viracor-IBT's laboratory in Lee's Summit, MO, or other laboratories designated by Viracor-IBT that are also certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform high complexity tests, 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 these specimens during the acute phase of infection (approximately 7 days in serum, possibly longer in urine, following onset of symptoms, if present).

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 "Viracor-IBT's laboratory in Lee's Summit, MO, or other laboratories designated by Viracor-IBT that are also certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform high complexity tests" 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 Zika Virus Real-time RT-PCR 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 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 Zika Virus Real-time RT-PCR test 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 Zika Virus Real-time RT-PCR test, 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 Zika Virus Real-time RT-PCR test 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 Zika Virus Real-time RT-PCR test 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 Zika Virus Real-time RT-PCR test 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 Zika Virus Real-time RT-PCR test

Viracor-IBT's Zika Virus Real-time RT-PCR test is a real-time reverse transcription PCR assay for the qualitative detection of RNA from Zika virus in serum, plasma, urine (collected alongside a patient-matched serum or plasma specimen) and other authorized specimen types.

To perform the Zika Virus Real-time RT-PCR test, samples are first extracted to isolate the Zika virus RNA. Nucleic acids are isolated and purified from the sample using either the bioMerieux NucliSENS easyMag extraction platform with the protocol for total nucleic acid extraction or 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.

The purified nucleic acid is first reverse transcribed into cDNAs and amplified using Life Technologies TaqPath™ 1-step RT-qPCR master mix reagent or other authorized ancillary products. In the amplification process, the probe anneals to the specific target sequence located between the forward and reverse primers. 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 a fluorescent signal. With each cycle, additional reporter dye molecules are cleaved from their respective probes, increasing the fluorescence intensity. The RT-PCR is performed on the Applied Biosystems® 7500 Real-Time PCR Instrument (Thermo Fisher Scientific) or other authorized instruments.

The Zika Virus Real-time RT-PCR test uses the following materials, or other authorized materials or ancillary products:

- Zika Virus Enzyme Mix
- Zika Virus Primer/Probe Mix
- Zika Virus Internal Control
- Zika Virus Negative Extraction Control
- Zika Virus Positive Extraction Control
- Zika Virus Positive Amplification Curve Controls
- Water (nuclease free)

The Zika Virus Real-time RT-PCR test requires the following control materials, or other authorized control materials, to be included in each run; all controls listed below must generate expected results in order for a test to be considered valid:

- Internal Control
    - The internal control consists of a bacteriophage MS2 that is added to each specimen prior to extraction, is co-purified with each specimen, and is amplified by a specific primers and probe set.
    - The internal control MS2 controls for sample extraction, reverse transcription, amplification and detection and also ensures the absence of non-specific PCR inhibition of a sample.

- No Template Control

  - RNase-, DNase-free water.
  - A no template control is included in each RT-PCR run of specimen extractions to monitor for Zika virus contamination.

- Zika Virus Negative Extraction Control
  - Known negative sample.
  - A negative extraction control is included in each run of specimen extractions to monitor for Zika virus contamination.

- Zika Virus Positive Extraction Control
  - Live Zika whole virus.
  - A positive control is included in each run of specimen extractions to monitor nucleic acid isolation and detection of Zika virus RNA.

- Zika Virus Positive Amplification Curve Controls
  - Modified plasmid with inserted nucleotide regions from the Zika strain KU497555 (Brazil, 2015) – high and low concentrations.
  - The positive amplification curve controls are included in each RT-PCR run of specimen extractions to demonstrate that the anticipated level of sensitivity has been achieved.

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

The above described Zika Virus Real-time RT-PCR test, when labeled consistently with the labeling authorized by FDA entitled "Zika Virus Real-time RT-PCR, Viracor-IBT Laboratories, Inc., Instructions for Use" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), which may be revised by Viracor-IBT 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 Zika Virus Real-time RT-PCR test 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 Viracor-IBT Laboratories, Inc.'s Zika Virus Real-time RT-PCR Test Results
- Fact Sheet for Pregnant Women: Understanding Results from the Viracor-IBT Laboratories, Inc.'s Zika Virus Real-time RT-PCR Test
- Fact Sheet for Patients: Understanding Results from the Viracor-IBT Laboratories, Inc.'s Zika Virus Real-time RT-PCR Test

As described in Section IV below, Viracor-IBT is also authorized to make available additional information relating to the emergency use of the authorized Zika Virus Real-time RT-PCR 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 Zika Virus Real-time RT-PCR test 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 Zika Virus Real-time RT-PCR test 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 Zika Virus Real-time RT-PCR test, 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 Zika Virus Real-time RT-PCR 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 Zika Virus Real-time RT-PCR test 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 a geographic region with active Zika virus transmission 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 Zika Virus Real-time RT-PCR 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 Zika Virus Real-time RT-PCR 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:

Viracor-IBT Laboratories, Inc. and Its Authorized Distributor(s)

A. Viracor-IBT and its authorized distributor(s) will distribute the authorized Zika Virus Real-time RT-PCR test with the authorized labeling, as may be revised by Viracor-IBT Laboratories, Inc. in consultation with DMD/OIR/CDRH, only to authorized laboratories.

B. Viracor-IBT and its authorized distributor(s) will provide to authorized laboratories the authorized Zika Virus Real-time RT-PCR test Fact Sheet for Health Care Providers, the authorized Zika Virus Real-time RT-PCR test Fact Sheet for Pregnant Women, and the authorized Zika Virus Real-time RT-PCR test Fact Sheet for Patients.

C. Viracor-IBT and its authorized distributor(s) will make available on their websites the authorized Zika Virus Real-time RT-PCR test Fact Sheet for Health Care Providers, the authorized Zika Virus Real-time RT-PCR test Fact Sheet for Pregnant Women, and the authorized Zika Virus Real-time RT-PCR test Fact Sheet for Patients.

D. Viracor-IBT 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. Viracor-IBT and its authorized distributor(s) will ensure that the authorized laboratories using the authorized Zika Virus Real-time RT-PCR test 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, Viracor-IBT and its authorized distributor(s) will maintain records of device usage.

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

H. Viracor-IBT and its authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized Zika Virus Real-

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

time RT-PCR test that is consistent with, and does not exceed, the terms of this letter of authorization.

Viracor-IBT Laboratories, Inc.

I. Viracor-IBT will notify FDA of any authorized distributor(s) of the Zika Virus Real-time RT-PCR test, including the name, address, and phone number of any authorized distributor(s).

J. Viracor-IBT 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. Viracor-IBT may request changes to the authorized Zika Virus Real-time RT-PCR test Fact Sheet for Health Care Providers, the authorized Zika Virus Real-time RT-PCR test Fact Sheet for Pregnant Women, and the authorized Zika Virus Real-time RT-PCR test Fact Sheet for Patients. Such requests will be made by Viracor-IBT in consultation with, and require concurrence of, DMD/OIR/CDRH.

L. Viracor-IBT may request the addition of other instruments for use with the authorized Zika Virus Real-time RT-PCR test. Such requests will be made by Viracor-IBT in consultation with, and require concurrence of, DMD/OIR/CDRH.

M. Viracor-IBT may request the addition of other extraction methods for use with the authorized Zika Virus Real-time RT-PCR test. Such requests will be made by Viracor-IBT in consultation with, and require concurrence of, DMD/OIR/CDRH.

N. Viracor-IBT may request the addition of other specimen types for use with the authorized Zika Virus Real-time RT-PCR test. Such requests will be made by Viracor-IBT in consultation with, and require concurrence of, DMD/OIR/CDRH.

O. Viracor-IBT may request the addition of other control materials for use with the authorized Zika Virus Real-time RT-PCR test. Such requests will be made by Viracor-IBT in consultation with, and require concurrence of, DMD/OIR/CDRH.

P. Viracor-IBT may request the addition of other materials and ancillary products for use with the authorized Zika Virus Real-time RT-PCR test. Such requests will be made by Viracor-IBT in consultation with, and require concurrence of, DMD/OIR/CDRH.

Q. Viracor-IBT will assess traceability[6] of the Zika Virus Real-time RT-PCR test with FDA recommended reference material(s). After submission to FDA and DMD/OIR/CDRH's review of and concurrence with the data, Viracor-IBT will update its labeling to reflect the additional testing.

R. Viracor-IBT 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 Zika Virus Real-time RT-PCR test 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 Zika Virus Real-time RT-PCR test on the Applied Biosystems® 7500 Real-Time PCR Instrument or other authorized instruments.

U. Authorized laboratories will perform the Zika Virus Real-time RT-PCR test using the bioMerieux NucliSENS easyMag extraction platform with the protocol for total nucleic acid extraction or with other authorized extraction methods.

V. Authorized laboratories will perform the Zika Virus Real-time RT-PCR test on serum, plasma, or urine (collected with 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 Viracor-IBT, 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.

Viracor-IBT Laboratories, Inc., Its Authorized Distributor(s) and Authorized Laboratories

Z. Viracor-IBT, 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 Zika Virus Real-time RT-PCR test 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.

BB. All advertising and promotional descriptive printed matter relating to the use of the authorized Zika Virus Real-time RT-PCR test shall clearly and conspicuously state

[7] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that Viracor-IBT 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/.

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 Zika Virus Real-time RT-PCR 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 Zika Virus Real-time RT-PCR 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,

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Robert M. Califf, M.D.
Commissioner of Food and Drugs

Enclosures