



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

October 7, 2016

Susan M. Schneider, RAC
Executive Director Quality & Regulatory
Affairs
Quest Diagnostics
2121 N. California Blvd., Suite #290
Walnut Creek, CA 94596

Dear Ms. Schneider:

On April 28, 2016, based on a request by Focus Diagnostics, Inc.¹, the Food and Drug Administration (FDA) issued a letter authorizing the emergency use of the Zika Virus RNA Qualitative Real-Time RT-PCR² test for the qualitative detection of RNA from Zika virus in human serum 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 qualified laboratories designated by Focus Diagnostics, Inc. and, in the United States, 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).³ 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 a current infection.

On September 28, 2016, FDA received a request from Focus Diagnostics, Inc. to amend the Emergency Use Authorization (EUA). In response to that request, and having concluded that revising the April 28, 2016, EUA is appropriate to protect the public health or safety under section 564(g)(2)(C) of the Act (21 U.S.C. § 360bbb-3(g)(2)(C)), the April 28, 2016, letter

¹ Focus Diagnostics, Inc. is a subsidiary of Quest Diagnostics.

² U.S. Food and Drug Administration (FDA). *Authorizations of Emergency Use of In Vitro Diagnostic Devices for Detection of Zika Virus; Availability*. 81 Fed. Reg. 39653 (June 17, 2016).

³ For ease of reference, this letter will refer to “qualified laboratories designated by Focus Diagnostics, Inc. and, in the United States, certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high complexity tests” as “authorized laboratories.”

authorizing the emergency use of the Zika Virus RNA Qualitative Real-Time RT-PCR test is being reissued in its entirety with the amendments incorporated.⁴

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.⁵ 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).⁶

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 RNA Qualitative 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 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 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 RNA Qualitative Real-Time RT-PCR 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;

⁴ The amendments to the April 28, 2016 letter: (1) allow use of a commercially sourced inactivated Zika virus as a positive control material in addition to the Zika virus strain FLR (live virus); (2) allow the addition of urine (when collected alongside a patient-matched serum specimen) as an authorized specimen type; (3) update the Instructions for Use with the results of the FDA Reference Material sensitivity studies; (4) combine the Pregnant Women and Patient Fact Sheets into one Patient Fact Sheet; and (5) enable, as described in Section IV (Conditions of Authorization) of this letter, certain changes or additions to be made by Focus Diagnostics, Inc. 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 authorized Instructions for Use and Fact Sheets also have been updated to incorporate these amendments, where applicable.

⁵ 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.

⁶ 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).

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the Zika Virus RNA Qualitative Real-Time RT-PCR, 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 RNA Qualitative Real-Time RT-PCR 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 RNA Qualitative Real-Time RT-PCR for detecting Zika virus and diagnosing Zika virus infection.⁷

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 RNA Qualitative Real-Time RT-PCR 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).

The Authorized Zika Virus RNA Qualitative Real-Time RT-PCR

Focus Diagnostics, Inc.'s Zika Virus RNA Qualitative Real-Time RT-PCR 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 epidemiological criteria for which Zika virus testing may be indicated). The Zika Virus RNA Qualitative Real-Time RT-PCR can also be used with other authorized specimen types. The test procedure consists of nucleic acid extraction using the Roche MagNA Pure LC Total Nucleic Acid Isolation Large Volume Kit on the Roche MagNA Pure LC System, or other authorized extraction method, followed by rRT-PCR on the Applied Biosystems (ABI) 7500 Real-Time PCR System or other authorized instruments, using the Life Technologies SuperScript[®] III Platinum[®] One-Step Quantitative RT-PCR System, or other authorized PCR enzyme Kits.

The Zika Virus RNA Qualitative Real-Time RT-PCR includes primers and dual-labeled hydrolysis (Taqman[®]) probes targeting two separate nucleotide sequences within the Zika virus genome to be used in the *in vitro* qualitative detection of Zika virus RNA isolated from human serum and urine (collected alongside a patient-matched serum specimen) and any other authorized specimens. The purified nucleic acids are first reverse transcribed into cDNAs. In

⁷ No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

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 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 Zika Virus RNA Qualitative Real-Time RT-PCR kit uses the following materials, or other authorized materials or ancillary products:

- Zika Virus RNA Qualitative Real-Time RT-PCR Primer and Probe sets for the detection of Zika virus and the Internal Control
 - ZV RTPCR Mix 1 (contains SuperScript® III reaction buffer, primers, and probes for the “M” region of the Zika virus genome and the Internal Control)
 - ZV RTPCR Mix 2 (contains SuperScript® III reaction buffer, primers, and probes for the “env” region of the Zika virus genome and the Internal Control)

The Zika Virus RNA Qualitative Real-Time RT-PCR requires the following control materials, or other authorized 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:

- **Zika Virus RNA Qualitative Real-Time RT-PCR Negative Control**
 - Normal human serum, no detectable Zika virus RNA
 - One included in each batch of specimen extraction to monitor Zika virus contamination
- **Zika Virus RNA Qualitative Real-Time RT-PCR Positive Control**
 - Zika virus strain FLR (live virus) or inactivated Zika virus diluted in normal human serum
 - One included in each batch of specimen extraction to monitor nucleic acid isolation and detection of Zika virus RNA
- **Zika Virus RNA Qualitative Real-Time RT-PCR Internal Control**
 - DNA target included in each specimen, Positive Control, and Negative Control
 - Consists of a portion of a plant genome, added to the lysis reagent provided in the MagNA Pure LC Total Nucleic Acid Large Volume Isolation Kit
 - Ensures the absence of non-specific PCR inhibition of a sample

The above described Zika Virus RNA Qualitative Real-Time RT-PCR, when labeled consistently with the labeling authorized by FDA entitled “Zika Virus RNA Qualitative Real-Time RT-PCR Instructions for Use” (available at <http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm>), which may be revised by Focus Diagnostics, Inc. in consultation with DMD/OIR/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 RNA Qualitative Real-Time RT-PCR 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, including pregnant women:

- Fact Sheet for Healthcare Providers: Interpreting Zika Virus RNA Qualitative Real-Time RT-PCR Test Results
- Fact Sheet for Patients: Understanding Results from the Zika Virus RNA Qualitative Real-Time RT-PCR Test

As described in Section IV below, Focus Diagnostics, Inc. and its authorized distributors are also authorized to make available additional information relating to the emergency use of the authorized Zika Virus RNA Qualitative Real-Time RT-PCR 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 RNA Qualitative Real-Time RT-PCR 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 RNA Qualitative Real-Time RT-PCR 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 RNA Qualitative Real-Time RT-PCR, 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 RNA Qualitative Real-Time RT-PCR 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 RNA Qualitative Real-Time RT-PCR 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 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 Zika Virus RNA Qualitative Real-Time RT-PCR 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 RNA Qualitative Real-Time RT-PCR.
- 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:

Focus Diagnostics, Inc. and Its Authorized Distributor(s)

- A. Focus Diagnostics, Inc. and its authorized distributor(s) will distribute the authorized Zika Virus RNA Qualitative Real-Time RT-PCR with the authorized labeling, as may be revised by Focus Diagnostics, Inc. in consultation with DMD/OIR/CDRH, only to authorized laboratories.
- B. Focus Diagnostics, Inc. and its authorized distributor(s) will provide to authorized laboratories the authorized Zika Virus RNA Qualitative Real-Time RT-PCR Fact Sheet for Healthcare Providers and the authorized Zika Virus RNA Qualitative Real-Time RT-PCR Fact Sheet for Patients.
- C. Focus Diagnostics, Inc. and its authorized distributor(s) will make available on their website(s) the authorized Zika Virus RNA Qualitative Real-Time RT-PCR Fact Sheet for Healthcare Providers and the authorized Zika Virus RNA Qualitative Real-Time RT-PCR Fact Sheet for Patients.
- D. Focus Diagnostics, Inc. 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. Focus Diagnostics, Inc. and its authorized distributor(s) will ensure that authorized laboratories using the authorized Zika Virus RNA Qualitative Real-Time RT-PCR have a process in place for reporting test results to healthcare providers and relevant public health authorities, as appropriate.⁸
- F. Through a process of inventory control, Focus Diagnostics, Inc. and its authorized distributor(s) will maintain records of device usage.
- G. Focus Diagnostics, Inc. and its authorized distributor(s) will collect information on the performance of the test. Focus Diagnostics, Inc. 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 Focus Diagnostics, Inc. becomes aware.
- H. Focus Diagnostics, Inc. and its authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized Zika Virus RNA Qualitative Real-Time RT-PCR that is consistent with, and does not exceed, the terms of this letter of authorization.

Focus Diagnostics, Inc.

- I. Focus Diagnostics, Inc. will notify FDA of any authorized distributor(s) of the Zika Virus Realtime RT-PCR test, including the name, address, and phone number of any authorized distributor(s).
- J. Focus Diagnostics, Inc. 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. Focus Diagnostics, Inc. may request changes to the authorized Zika Virus RNA Qualitative Real-Time RT-PCR Fact Sheet for Healthcare Providers and the authorized Zika Virus RNA Qualitative Real-Time RT-PCR Fact Sheet for Patients. Such requests will be made by Focus Diagnostics, Inc., and require concurrence of, DMD/OIR/CDRH.
- L. Focus Diagnostics, Inc. may request the addition of other instruments for use with the authorized Zika Virus RNA Qualitative Real-Time RT-PCR. Such requests will be made by Focus Diagnostics, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.

⁸ For questions related to reporting Zika test results to relevant public health authorities, it is recommended that Focus Diagnostics, Inc., authorized distributors, and authorized laboratories consult with the applicable country, state or territory health department(s) and/or CDC. According to CDC, Zika is a nationally notifiable condition. <http://www.cdc.gov/zika/>.

- M. Focus Diagnostics, Inc. may request the addition of other extraction methods for use with the authorized Zika Virus RNA Qualitative Real-Time RT-PCR. Such requests will be made by Focus Diagnostics, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.
- N. Focus Diagnostics, Inc. may request the addition of other specimen types for use with the authorized Zika Virus RNA Qualitative Real-Time RT-PCR. Such requests will be made by Focus Diagnostics, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.
- O. Focus Diagnostics may request the addition of other control materials for use with the authorized Zika Virus RNA Qualitative Real-Time RT-PCR. Such requests will be made by Focus Diagnostics Inc., in consultation with, and require concurrence of, DMD/OIR/CDRH.
- P. Focus Diagnostics may request the addition and/or substitution of other materials and ancillary products for use with the authorized Zika Virus RNA Qualitative Real-Time RT-PCR. Such requests will be made by Focus Diagnostics in consultation with, and require concurrence of, DMD/OIR/CDRH.
- Q. Focus Diagnostics, Inc. will assess traceability⁹ of the Zika Virus RNA Qualitative Real-Time RT-PCR with FDA recommended reference material(s). After submission to FDA and DMD/OIR/CDRH's review of and concurrence with the data, Focus Diagnostics, Inc. will update its labeling to reflect the additional testing.
- R. Focus Diagnostics, Inc. will track adverse events and report to FDA under 21 CFR Part 803, but can submit reports to FDA in paper form.

Authorized Laboratories

- S. Authorized laboratories will include with reports of the results of the Zika Virus RNA Qualitative Real-Time RT-PCR the authorized Fact Sheet for Healthcare Providers 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 RNA Qualitative Real-Time RT-PCR on the Applied Biosystems (ABI) 7500 Real-Time PCR Instrument or other authorized instruments.
- U. Authorized laboratories will perform the Zika Virus RNA Qualitative Real-Time RT-PCR using the Roche MagNA Pure LC Total Nucleic Acid Isolation Large Volume Kit on the Roche MagNA Pure LC System extraction methods, or with other authorized extraction methods.

⁹ Traceability refers to tracing analytical sensitivity/reactivity back to a FDA recommended reference material.

- V. Authorized laboratories will perform the Zika Virus RNA Qualitative Real-Time RT-PCR on serum and urine (collected alongside a patient-matched serum specimen) or with other authorized specimen types.
- W. Authorized laboratories will have a process in place for reporting test results to healthcare providers and relevant public health authorities, as appropriate.¹⁰
- X. Authorized laboratories will collect information on the performance of the test and report to Focus Diagnostics, Inc., 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.

Focus Diagnostics, Inc., Its Authorized Distributor(s) and Authorized Laboratories

- Z. Focus Diagnostics, Inc., 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 RNA Qualitative Real-Time RT-PCR 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 RNA Qualitative Real-Time RT-PCR 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 not for any other viruses or pathogens; and

¹⁰ For questions related to reporting Zika test results to relevant public health authorities, it is recommended that Focus Diagnostics, Inc., authorized distributors, and authorized laboratories consult with the applicable country, state or territory health department(s) and/or CDC. According to CDC, Zika is a nationally notifiable condition. <http://www.cdc.gov/zika/>.

- 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 RNA Qualitative Real-Time RT-PCR 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 RNA Qualitative Real-Time RT-PCR 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,

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

Enclosures