DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

June 29, 2016

Thomas R. Frieden, M.D., M.P.H.
Director
Centers for Disease Control and Prevention
1600 Clifton Rd, MS D-14
Atlanta, GA 30333

Dear Dr. Frieden:

On February 26, 2016, based on a request by the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA) issued a letter authorizing the emergency use of the Zika Immunoglobulin M (IgM) Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA)[1] for the presumptive detection of Zika virus-specific IgM in human sera or cerebrospinal fluid (CSF) that is submitted alongside a patient-matched serum specimen from individuals meeting CDC Zika virus clinical criteria (e.g., a history of clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., recent history of 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 as part of a public health response), by qualified laboratories designated by CDC 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,[2] pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3). Where there are positive or equivocal results from the Zika MAC-ELISA, confirmation of the presence of anti-Zika IgM antibodies requires additional testing by CDC, or by authorized laboratories in consultation with CDC, using the CDC-issued algorithm.

On June 21, 2016, FDA received a request from CDC to amend the Emergency Use Authorization (EUA). In response to that request, and having concluded that revising the February 26, 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 February 26, 2016, letter authorizing the emergency use of the Zika MAC-ELISA is being reissued in its entirety with the amendments incorporated.[3]

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[1] U.S. Food and Drug Administration (FDA). *Authorization of Emergency Use of an In Vitro Diagnostic Device for Diagnosis of Zika Virus Infection; Availability*. 81 Fed. Reg. 17170 (March 28, 2016).

[2] For ease of reference, this letter will refer to "qualified laboratories designated by CDC 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."

[3] The amendments to the February 26, 2016, letter: (1) update the language for the Centers for Disease Control and Prevention (CDC) Zika virus clinical and epidemiological criteria; (2) update the language related to additional testing of positive or equivocal test results using the CDC-issued algorithm; (3) allow for CDC to develop additional Fact Sheets for health care providers, pregnant women, and other patients in consultation with, and with concurrence of, FDA's Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist

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.[4] 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).[5]

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 MAC-ELISA (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 presumptive 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 MAC-ELISA for the presumptive detection of Zika virus-specific IgM antibodies in the specified population meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

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

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the Zika MAC-ELISA may be effective in diagnosing Zika virus infection when positive or equivocal results are considered in conjunction with additional testing using the CDC-issued algorithm and/or are considered alongside test results for other patient-matched specimens using the CDC-issued algorithm, and that the known and potential benefits of the Zika MAC-ELISA for diagnosing Zika virus infection outweigh the

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(OCS)/Office of the Commissioner (OC) and Division of Microbiology Devices (DMD)/Office of In Vitro Diagnostics and Radiological Health (OIR)/Center for Devices and Radiological Health (CDRH); (4) allow use of Zika COS-1 Recombinant Antigen (CDC catalog #AV0005) as Zika Viral Antigen in addition to Lyophilized Zika Vero E6 Tissue Culture Antigen (CDC catalog #AV002 or AV003); and (5) as described in Section IV. Conditions of Authorization of this letter enable certain changes or additions to be made by CDC in consultation with, and with concurrence of, DMD/OIR/CDRH. The authorized Instructions for Use and Fact Sheets also have been updated to incorporate these amendments, where applicable.

[4] 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.

[5] 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).

known and potential risks of such product when positive or equivocal results are considered in conjunction with additional testing using the CDC-issued algorithm and/or are considered alongside test results for other patient-matched specimens using the CDC-issued algorithm; and

3. There is no adequate, approved, and available alternative to the emergency use of the Zika MAC-ELISA for diagnosing Zika virus infection.[6]

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 MAC-ELISA by authorized laboratories for the presumptive detection of Zika virus-specific IgM antibodies in individuals meeting CDC Zika virus clinical criteria (e.g., clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiologic criteria for which Zika virus testing may be indicated) where positive or equivocal results are considered in conjunction with additional testing using the CDC-issued algorithm and/or are considered alongside test results for other patient-matched specimens using the CDC-issued algorithm.

The Authorized Zika MAC-ELISA

The Zika MAC-ELISA is an IgM antibody capture enzyme-linked immunosorbent assay for the *in vitro* qualitative detection of Zika virus-specific IgM antibodies in human sera and other authorized specimen types from individuals meeting CDC Zika virus clinical criteria (e.g., clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiologic criteria for which Zika virus testing may be indicated). The Zika MAC-ELISA can also be used with CSF specimens that are submitted alongside a patient-matched serum specimen and other authorized specimen types. The test procedure is based on capturing human IgM antibodies from the patient specimen on a microtiter plate using anti-human-IgM antibody followed by the addition of Zika virus specific antigen and detector conjugate.

One of the limitations of this test is the possibility of false positive results in patients with a history of infection with other flaviviruses. Additional testing of equivocal and positive specimens and/or other patient-matched specimens, as specified in the CDC-issued algorithm, is therefore required to confirm Zika virus infection.

The assay uses a purified antibody specific for human IgM that is immobilized on a test plate to capture IgM antibodies from a human specimen. A serum or CSF specimen from a patient is added to the test plate, and IgM antibodies from the specimen bind to the immobilized antibody. After washing, cultured Zika virus antigen is added and binds to any Zika virus-specific IgM antibodies captured on the plate. A flavivirus specific monoclonal antibody conjugated to horseradish peroxidase is then added. Upon addition of substrate, conjugate that is bound to any

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

immobilized Zika antigen will catalyze a colorimetric reaction that can be measured by a spectrophotometer or other instruments that may be authorized.

The Zika MAC-ELISA includes the following materials (the following authorized antigens may be substituted or changed 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)):

- Normal Antigen (any of the following products are acceptable for use in the assay):
    - Lyophilized Normal Vero E6 Antigen (CDC catalog #AV0001)
    - Lyophilized Normal Control COS-1 Recombinant Antigen (CDC catalog #AV0006)

- Zika Viral Antigen (any of the following products is acceptable for use in the assay):
    - Lyophilized Zika Vero E6 Tissue Culture Antigen (CDC catalog #AV002 or AV003) consisting of Zika antigen prepared specifically for use in the Zika MAC-ELISA
    - Zika COS-1 Recombinant Antigen (CDC catalog #AV0005) consisting of non-infectious Zika virus-like particles prepared for use in the Zika MAC-ELISA

- Lyophilized Flavivirus IgM Positive Control (CDC catalog #AV004), a chimeric monoclonal antibody specific for flaviviruses

The Zika MAC-ELISA requires the following control materials or other authorized control materials:

- Positive Control:

  Flavivirus IgM Positive Control: This product is a flavivirus group reactive humanized IgM antibody used to establish the Positive Control P/N ratio, which validates the plate run. This control is included in the Zika MAC-ELISA.

- Negative Controls:

  Normal Vero E6 Antigen: This control is used to measure the background signal generated by each specimen. This control is included in the Zika MAC-ELISA.

  Negative control serum: The negative control serum (tested negative for Zika virus) is non-reactive with viral antigen and is used to establish the Specimen P/N ratio, which also validates the plate run. This control is not included in the Zika MAC-ELISA.

Controls listed above must be included on each 96-well plate. Controls must generate expected results in order for a plate to be considered valid.

The Zika MAC-ELISA also requires the use of the following additional materials and ancillary reagents as described in the authorized Zika MAC-ELISA Instructions for Use:

- 96-well plate
- Detecting antibody conjugate: Horseradish peroxidase conjugated monoclonal antibody 6B6C-1, specific for human IgM
- Goat anti-human IgM
- Negative control serum
- Enhanced K-Blue TMB substrate (3,3', 5, 5' tetramethylbenzidine base)

The above described Zika MAC-ELISA, when labeled consistently with the labeling authorized by FDA entitled "Zika MAC-ELISA Instructions for Use" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), is authorized to be distributed to and used by authorized laboratories under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law. This labeling may be revised by CDC through consultation with, and with concurrence of, DMD/OIR/CDRH.

The above described Zika MAC-ELISA 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 Zika MAC-ELISA Results
- Fact Sheet for Pregnant Women: Understanding Results from the Zika MAC-ELISA
- Fact Sheet for Patients: Understanding Results from the Zika MAC-ELISA

Other Fact Sheets developed by CDC in consultation with, and with concurrence of, the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC) and DMD/OIR/CDRH may be authorized to accompany the above described Zika MAC-ELISA and to be made available to health care providers, pregnant women, and other patients.

As described in Section IV below, CDC is also authorized to make available additional information relating to the emergency use of the authorized Zika MAC-ELISA 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 MAC-ELISA in the specified population, when used for presumptive detection of Zika virus-specific IgM antibodies and used consistently with the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of such a product.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the authorized Zika MAC-ELISA may be effective in the 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 MAC-ELISA, when used to diagnose Zika virus infection in the specified population (as described in the Scope of Authorization of this letter (Section II)), meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized Zika MAC-ELISA 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 MAC-ELISA described above is authorized to diagnose Zika virus infection in individuals meeting CDC Zika virus clinical criteria (e.g., clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other 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 MAC-ELISA 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 MAC-ELISA.

- 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:

Centers for Disease Control and Prevention (CDC)

A. CDC will distribute the authorized Zika MAC-ELISA with the authorized labeling only to authorized laboratories.[7] CDC may request changes to the authorized labeling.

[7] Current stocks of CDC Zika MAC-ELISA products previously distributed to authorized laboratories and labeled as

Such requests will be made by CDC in consultation with, and require concurrence of, DMD/OIR/CDRH.

B. CDC will provide to authorized laboratories the authorized Zika MAC-ELISA Fact Sheet for Health Care Providers, the authorized Zika MAC-ELISA Fact Sheet for Pregnant Women, and the authorized Zika MAC-ELISA Fact Sheet for Patients, and any additional Zika MAC-ELISA Fact Sheets for Health Care Providers, Pregnant Women, and Patients that OCET/OCS/OC and DMD/OIR/CDRH may authorize.

C. CDC will make available on its website the authorized Zika MAC-ELISA Fact Sheet for Health Care Providers, the authorized Zika MAC-ELISA Fact Sheet for Pregnant Women, and the authorized Zika MAC-ELISA Fact Sheet for Patients, and any additional Zika MAC-ELISA Fact Sheets for Health Care Providers, Pregnant Women, and Patients that OCET/OCS/OC and DMD/OIR/CDRH may authorize.

D. CDC will inform authorized laboratories and relevant public health authority(ies) of this EUA, including the terms and conditions herein.

E. CDC will ensure that authorized laboratories using the authorized Zika MAC-ELISA have a process in place for reporting test results to health care providers and relevant public health authorities, as appropriate.[8]

F. CDC will track adverse events and report to FDA under 21 CFR Part 803.

G. Through a process of inventory control, CDC will maintain records of device usage.

H. CDC will collect information on the performance of the assay. CDC will report to FDA any suspected occurrence of false negative results and significant deviations from the established performance characteristics of the assay of which CDC becomes aware.

I. CDC is authorized to make available additional information relating to the emergency use of the authorized Zika MAC-ELISA that is consistent with, and does not exceed, the terms of this letter of authorization.

J. CDC may request changes to the authorized Zika MAC-ELISA Fact Sheet for Health Care Providers, the authorized Zika MAC-ELISA Fact Sheet for Pregnant Women, and the authorized Zika MAC-ELISA Fact Sheet for Patients. CDC may also request that CDC develop new Zika MAC-ELISA Fact Sheets for Health Care Providers, Pregnant Women, and Patients, if appropriate, and may request changes to such Fact Sheets. All such requests listed in this condition of authorization will be made by CDC in consultation with, and require concurrence of, OCET/OCS/OC and DMD/OIR/CDRH.

"Research Use Only" may be used by such laboratories for research use and/or diagnostic purposes under this authorization in accordance with the authorized Instructions for Use for the CDC Zika MAC-ELISA. Such stocks used for diagnostic purposes must be used in accordance with the conditions of this authorization.

[8] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that CDC and authorized laboratories consult with the applicable country, state, or territory health department(s). According to CDC, Zika is a nationally notifiable condition. https://wwwn.cdc.gov/nndss/conditions/notifiable/2016/.

K. CDC may request the addition of other instruments for use with the authorized Zika MAC-ELISA. Such requests will be made by CDC in consultation with, and require concurrence of, DMD/OIR/CDRH.

L. CDC may request the addition of other ancillary reagents for use with the authorized Zika MAC-ELISA. Such requests will be made by CDC in consultation with, and require concurrence of, DMD/OIR/CDRH.

M. CDC may request the addition of other specimen types for use with the authorized Zika MAC-ELISA. Such requests will be made by CDC in consultation with, and require concurrence of, DMD/OIR/CDRH.

N. CDC may request the addition of other control materials for use with the authorized Zika MAC-ELISA. Such requests will be made by CDC in consultation with, and require concurrence of, DMD/OIR/CDRH.

O. CDC may request change of the CDC-issued algorithm used for confirmatory testing of Zika MAC-ELISA equivocal and presumptive positive results. Such requests will be made by CDC in consultation with, and require concurrence of, DMD/OIR/CDRH.

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

Authorized Laboratories

Q. Authorized laboratories will include with reports of the results of the Zika MAC-ELISA, the authorized Fact Sheet for Health Care Providers, the authorized Fact Sheet for Pregnant Women, and the authorized Fact Sheet for Patients, and any additional Zika MAC-ELISA Fact Sheets for Health Care Providers, Pregnant Women, and Patients that OCET/OCS/OC and DMD/OIR/CDRH may authorize. Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.

R. Within the United States and its territories, authorized laboratories will report all equivocal and presumptive positive results to CDC.

S. Authorized laboratories will have a process in place to assure that positive or equivocal results are considered in conjunction with additional testing, and/or are considered alongside test results for other patient-matched specimens, using the CDC-issued algorithm.

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

[9] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that CDC and authorized laboratories consult with the applicable country, state, or territory health department(s). According to CDC, Zika is a nationally notifiable condition. https://wwwn.cdc.gov/nndss/conditions/notifiable/2016/.

U. Authorized laboratories will collect information on the performance of the assay and report to CDC any suspected occurrence of false negative results and significant deviations from the established performance characteristics of which they become aware.

V. All laboratory personnel using the assay should be appropriately trained in performing and interpreting immunoassays techniques, use appropriate laboratory and personal protective equipment when handling this kit, and use the test in accordance with the authorized labeling.

CDC and Authorized Laboratories

W. CDC 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

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

Y. All advertising and promotional descriptive printed matter relating to the use of the authorized Zika MAC-ELISA shall clearly and conspicuously state that:

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

No advertising or promotional descriptive printed matter relating to the use of the authorized Zika MAC-ELISA 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 MAC-ELISA 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