



August 4, 2016

Mr. Roy Johnson
Manager, Regulatory Affairs
Luminex Corporation
12212 Technology Blvd.
Austin, TX 78727

Dear Mr. Johnson:

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 Luminex Corporation's ("Luminex") xMAP[®] MultiFLEX[™] Zika RNA Assay for the qualitative detection of RNA from Zika virus in human serum, plasma, and urine (collected alongside a patient-matched serum or plasma specimen) from individuals meeting Centers for Disease Control and Prevention (CDC) Zika virus clinical criteria (e.g., clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological 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 virus RNA. Zika virus RNA is generally detectable in these specimens during the acute phase of infection and, according to the updated CDC Guidance for U.S. Laboratories Testing for Zika Virus Infection², up to 14 days in serum and urine (possibly longer in urine), following onset of symptoms, if present. Positive results are indicative of current infection.

On February 26, 2016, pursuant to section 564(b)(1)(C) of the Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of Health and Human Services (HHS) determined that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad and that involves Zika virus.³ 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

¹ For ease of reference, this letter will refer to "laboratories in the United States (U.S.) that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high complexity tests, or by similarly qualified non-U.S. laboratories" as "authorized laboratories."

² Available at <http://www.cdc.gov/zika/laboratories/lab-guidance.html> (last updated on July 26, 2016).

³ 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.

and/or diagnosis of Zika virus infection, subject to the terms of any authorization issued under 21 U.S.C. § 360bbb-3(a).⁴

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 xMAP[®] MultiFLEX[™] Zika RNA Assay (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 xMAP[®] MultiFLEX[™] Zika RNA Assay 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 xMAP[®] MultiFLEX[™] Zika RNA Assay, 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 xMAP[®] MultiFLEX[™] Zika RNA Assay 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 xMAP[®] MultiFLEX[™] Zika RNA Assay for detecting Zika virus and diagnosing Zika virus infection.⁵

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 xMAP[®] MultiFLEX[™] Zika RNA Assay 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 epidemiological criteria for which Zika virus testing may be indicated).

⁴ 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).

⁵ No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

The Authorized xMAP® MultiFLEX™ Zika RNA Assay

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

To perform the xMAP® MultiFLEX™ Zika RNA Assay, samples are first extracted to isolate the Zika virus RNA. Nucleic acids are isolated and purified from the sample using the BioMerieux's NucliSENS easyMag nucleic acid extraction system, 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.

Extracted total nucleic acid is then simultaneously amplified using target specific primers and probes for RT-PCR followed by amplicon hybridization to probe-coupled microspheres. Streptavidin-conjugated R-Phycoerythrin (SAPE) is added, and detection of the targets of interest is performed on a Luminex IVD xMAP instrument (MAGPIX or Luminex 100/200) or other authorized instruments.

The xMAP® MultiFLEX™ Zika RNA Assay includes the following materials, or other authorized materials or ancillary products:

- Primer Mix
- Streptavidin-Phycoerythrin (SAPE)
- Microsphere mix
- Buffer A
- Buffer B
- MS2 bacteriophage RNA extraction control

The xMAP® MultiFLEX™ Zika RNA Assay requires the following control materials, or other authorized control materials; all assay controls listed below must generate expected results in order for a test to be considered valid:

- Internal Control (Bacteriophage MS2)

This internal positive control is added to each test sample as well as to each external control prior to extraction. The internal control allows the user to ascertain whether the extraction and reverse-transcription/ amplification steps of the assay are functioning correctly.

- No Template Control (NTC)

No Template Controls (NTCs) for the amplification/ detection steps are DNase- and RNase-free distilled water in place of specimen nucleic acids and must be included in each assay run. The NTC is a control for contamination or improper function of the assay reagents which could result in false positive results.

- External Positive Control

An External Positive Control may be used with the xMAP® MultiFLEX™ Zika RNA Assay based on local guidelines or laboratory standard operating procedures (SOPs). The External

Positive Control should be processed with the same workflow as clinical specimens. A positive result for the Zika virus specific RNA confirms the assay is performing as expected.

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

The above described xMAP® MultiFLEX™ Zika RNA Assay, when labeled consistently with the labeling authorized by FDA entitled “xMAP® MultiFLEX™ Zika RNA Assay Instructions for Use” (available at <http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm>), which may be revised by Luminex 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 xMAP® MultiFLEX™ Zika RNA Assay 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 xMAP® MultiFLEX™ Zika RNA Assay Results
- Fact Sheet for Pregnant Women: Understanding Results from the xMAP® MultiFLEX™ Zika RNA Assay
- Fact Sheet for Patients: Understanding Results from the xMAP® MultiFLEX™ Zika RNA Assay

As described in Section IV below, Luminex is also authorized to make available additional information relating to the emergency use of the authorized xMAP® MultiFLEX™ Zika RNA Assay 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 xMAP® MultiFLEX™ Zika RNA Assay 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 xMAP® MultiFLEX™ Zika RNA Assay 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 xMAP® MultiFLEX™ Zika RNA Assay, 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 xMAP® MultiFLEX™ Zika RNA Assay 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 xMAP® MultiFLEX™ Zika RNA Assay 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 xMAP® MultiFLEX™ Zika RNA Assay 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 xMAP® MultiFLEX™ Zika RNA Assay.
- 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:

Luminex Corporation and Its Authorized Distributor(s)

- A. Luminex and its authorized distributor(s) will distribute the authorized xMAP® MultiFLEX™ Zika RNA Assay with the authorized labeling, as may be revised by Luminex in consultation with DMD/OIR/CDRH, only to authorized laboratories.
- B. Luminex and its authorized distributor(s) will provide to authorized laboratories the authorized xMAP® MultiFLEX™ Zika RNA Assay Fact Sheet for Health Care Providers, the authorized xMAP® MultiFLEX™ Zika RNA Assay for Pregnant

Women, and the authorized xMAP® MultiFLEX™ Zika RNA Assay Fact Sheet for Patients.

- C. Luminex and its authorized distributor(s) will make available on their websites the authorized xMAP® MultiFLEX™ Zika RNA Assay Fact Sheet for Health Care Providers, the authorized xMAP® MultiFLEX™ Zika RNA Assay Fact Sheet for Pregnant Women, and the authorized xMAP® MultiFLEX™ Zika RNA Assay Fact Sheet for Patients.
- D. Luminex 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. Luminex and its authorized distributor(s) will ensure that authorized laboratories using the authorized xMAP® MultiFLEX™ Zika RNA Assay have a process in place for reporting test results to health care providers and relevant public health authorities, as appropriate.⁶
- F. Through a process of inventory control, Luminex and its authorized distributor(s) will maintain records of device usage.
- G. Luminex and its authorized distributor(s) will collect information on the performance of the test. Luminex 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 Luminex becomes aware.
- H. Luminex and its authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized xMAP® MultiFLEX™ Zika RNA Assay that is consistent with, and does not exceed, the terms of this letter of authorization.

Luminex Corporation

- I. Luminex will notify FDA of any authorized distributor(s) of the xMAP® MultiFLEX™ Zika RNA Assay, including the name, address, and phone number of any authorized distributor(s).
- J. Luminex 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. Luminex may request changes to the authorized xMAP® MultiFLEX™ Zika RNA Assay for Health Care Providers, the authorized xMAP® MultiFLEX™ Zika RNA Assay Fact Sheet for Pregnant Women, and the authorized xMAP® MultiFLEX™

⁶ For questions related to reporting Zika test results to relevant public health authorities, it is recommended that Luminex and authorized laboratories consult with the applicable country, state or territory health department(s). According to CDC, Zika virus disease is a nationally notifiable condition (see <http://www.cdc.gov/zika/>).

Zika RNA Assay Fact Sheet for Patients. Such requests will be made by Luminex in consultation with, and require concurrence of, DMD/OIR/CDRH.

- L. Luminex may request the addition of other instruments for use with the authorized xMAP® MultiFLEX™ Zika RNA Assay. Such requests will be made by Luminex in consultation with, and require concurrence of, DMD/OIR/CDRH.
- M. Luminex may request the addition of other extraction methods for use with the authorized xMAP® MultiFLEX™ Zika RNA Assay. Such requests will be made by Luminex in consultation with, and require concurrence of, DMD/OIR/CDRH.
- N. Luminex may request the addition of other specimen types for use with the authorized xMAP® MultiFLEX™ Zika RNA Assay. Such requests will be made by Luminex in consultation with, and require concurrence of, DMD/OIR/CDRH.
- O. Luminex may request the addition of other control materials for use with the authorized xMAP® MultiFLEX™ Zika RNA Assay. Such requests will be made by Luminex in consultation with, and require concurrence of, DMD/OIR/CDRH.
- P. Luminex may request the addition of other materials and ancillary reagents for use with the authorized xMAP® MultiFLEX™ Zika RNA Assay. Such requests will be made by Luminex in consultation with, and require concurrence of, DMD/OIR/CDRH.
- Q. Luminex will assess traceability⁷ of the xMAP® MultiFLEX™ Zika RNA Assay with FDA-recommended reference material(s). After submission to FDA and DMD/OIR/CDRH's review of and concurrence with the data, Luminex will update its labeling to reflect the additional testing.
- R. Luminex will track adverse events and report to FDA under 21 CFR Part 803.

Authorized Laboratories

- S. Authorized laboratories will include with reports of the results of the xMAP® MultiFLEX™ Zika RNA Assay 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 xMAP® MultiFLEX™ Zika RNA Assay on a Luminex IVD xMAP instrument (MAGPIX or Luminex 100/200) or other authorized instruments.
- U. Authorized laboratories will perform the xMAP® MultiFLEX™ Zika RNA Assay using the BioMerieux's NucliSENS easyMag nucleic acid extraction system or other authorized extraction methods.

⁷ Traceability refers to tracing analytical sensitivity/reactivity back to a FDA recommended reference material.

- V. Authorized laboratories will perform the xMAP® MultiFLEX™ Zika RNA Assay on serum, plasma, or urine (collected alongside a patient-matched serum or plasma specimen) or with other authorized specimen types.
- W. Authorized laboratories will have a process in place for reporting test results to health care providers and relevant public health authorities, as appropriate.⁸
- X. Authorized laboratories will collect information on the performance of the test and report to Luminex, 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.

Luminex Corporation, its Authorized Distributor(s) and Authorized Laboratories

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

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

No advertising or promotional descriptive printed matter relating to the use of the authorized xMAP® MultiFLEX™ Zika RNA Assay may represent or suggest that this test is safe or effective for the diagnosis of Zika virus infection.

The emergency use of the authorized xMAP® MultiFLEX™ Zika RNA Assay 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