2DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

August 26, 2016

Jintao Chen, Ph.D.
Director, Regulatory Affairs
Roche Molecular Systems, Inc.
4300 Hacienda Drive
Pleasanton, CA 94588

Dear Dr. Chen:

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 Roche Molecular Systems, Inc.'s *LightMix® Zika rRT-PCR Test* for the qualitative detection of RNA from Zika virus in human serum and EDTA plasma 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 (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, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3).[1] Test 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 Infection,[2] approximately 7 days following onset of symptoms, if present. Positive results are indicative of current infection.

On February 26, 2016, pursuant to section 564(b)(1)(C) of the Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of Health and Human Services (HHS) determined that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of 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 August 24, 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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-PCR Test*, when used with the specified instrument(s) 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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-PCR Test* 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 *LightMix® Zika rRT-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 epidemiological criteria for which Zika virus testing may be indicated).

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[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 *LightMix® Zika rRT-PCR Test*

The *LightMix® Zika rRT-PCR Test* is a real-time reverse transcription polymerase chain reaction (rRT-PCR) assay for the qualitative detection of RNA from Zika virus in human serum, EDTA plasma, and other authorized specimen types.

To perform the *LightMix® Zika rRT-PCR Test*, specimens are first extracted to isolate the Zika virus RNA. Nucleic acids are isolated and purified from the sample using either the automated Roche MagNA Pure 96 System together with the Roche MagNA Pure 96 DNA and Viral NA Large Volume reagent kit or the MagNA Pure Compact Instrument and MagNA Pure Compact Nucleic Acid Isolation Kit I - Large Volume, or other authorized extraction methods.

The purified RNA is reverse transcribed into cDNA, which is then amplified. The Roche LightCycler® Multiplex RNA Virus Master reagent, which contains reagents and enzymes for reverse transcription and specific amplification of the Zika virus targeted region, is added. The rRT-PCR is performed on the Roche LightCycler® 480 Instrument II, Roche cobas z 480 Analyzer (open channel) or other authorized instruments.

The *LightMix® Zika rRT-PCR Test* includes the following materials, or other authorized materials:

- **LightMix® Zika rRT-PCR Test PSR (1 Vial):** Contains pathogen-specific reagent (PSR), i.e., lyophilized primers and FAM-labeled probe that specifically detect Zika viral RNA.

- **LightMix® Zika rRT-PCR Test ivRNA Positive Control (1 Vial):** Contains lyophilized synthetic RNA, designed to react with the LightMix® Zika rRT-PCR Test PSR to indicate whether the *LightMix® Zika rRT-PCR Test* has worked properly.

The *LightMix® Zika rRT-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, as outlined in the *LightMix® Zika rRT-PCR Test* Instructions for Use:

- **Negative Process Control:** PCR-grade water is used in place of clinical samples from the beginning of the sample extraction process. The Negative Process Control is run in parallel with clinical specimens in each specimen extraction run.

- **Negative rRT-PCR Control:** PCR-grade water is used at the rRT-PCR step to test for absence of cross-contamination.

- **Positive Control:** Contains a synthetic RNA transcript containing the virus region targeted by the *LightMix® Zika rRT-PCR Test*. The Positive Control is used starting at the rRT-PCR step, then run in parallel with clinical specimens and the negative controls in each assay run.

- **Extraction Control:** The Extraction Control is the Roche RNA Process Control LSR (RPC). The Extraction Control is run together with every clinical specimen from the

beginning of the extraction process and is detected by rRT-PCR using a primer pair and a Cy5-labeled probe that are different from the Zika virus specific primer pair and probe.

The *LightMix® Zika rRT-PCR Test* also requires the use of additional materials and ancillary reagents commonly used in clinical laboratories and that are described in the authorized *LightMix® Zika rRT-PCR Test* Instructions for Use.

The above described *LightMix® Zika rRT-PCR Test*, when labeled consistently with the labeling authorized by FDA entitled "Instructions for Use: LightMix® Zika rRT-PCR Test" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), which may be revised by Roche Molecular Systems, Inc. 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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-PCR Test* Results
- Fact Sheet for Pregnant Women: Understanding Results from the *LightMix® Zika rRT-PCR Test*
- Fact Sheet for Patients: Understanding Results from the *LightMix® Zika rRT-PCR Test*

As described in Section IV below, Roche Molecular Systems, Inc., Roche Diagnostics, and other authorized distributer(s) are also authorized to make available additional information relating to the emergency use of the authorized *LightMix® Zika rRT-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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-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 geographic regions with 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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-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[6]

Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

Roche Molecular Systems, Inc., Roche Diagnostics, and/or Other Authorized Distributor(s)[7]

[6] Unless otherwise specified, Roche Molecular Systems, Inc. and Roche Diagnostics are the responsible parties for satisfying the Conditions of Authorization.

[7] At the time of authorization, Roche Diagnostics is the sole authorized distributer of the *LightMix® Zika rRT-PCR Test*, manufactured by TIB MOLBIOL GmbH.

A. Roche Diagnostics and other authorized distributor(s) will distribute the authorized *LightMix® Zika rRT-PCR Test* with the authorized labeling only to authorized laboratories. Changes to the authorized labeling may be made by Roche Molecular Systems, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.

B. Roche Diagnostics and other authorized distributor(s) will provide to authorized laboratories the authorized *LightMix® Zika rRT-PCR Test* Fact Sheet for Health Care Providers, the authorized *LightMix® Zika rRT-PCR Test* Fact Sheet for Pregnant Women, and the authorized *LightMix® Zika rRT-PCR Test* Fact Sheet for Patients.

C. Roche Diagnostics and other authorized distributor(s) will make available on their websites the authorized *LightMix® Zika rRT-PCR Test* Fact Sheet for Health Care Providers, the authorized *LightMix® Zika rRT-PCR Test* Fact Sheet for Pregnant Women, and the authorized *LightMix® Zika rRT-PCR Test* Fact Sheet for Patients.

D. Roche Diagnostics and other authorized distributor(s) will inform authorized laboratories and relevant public health authority(ies) of this EUA, including the terms and conditions herein.

E. Roche Diagnostics and other authorized distributor(s) will ensure that the authorized laboratories using the authorized *LightMix® Zika rRT-PCR Test* have a process in place for reporting test results to health care providers and relevant public health authorities, as appropriate.[8]

F. Through a process of inventory control, Roche Diagnostics and other authorized distributor(s) will maintain records of device usage.

G. Roche Diagnostics and other authorized distributor(s) will collect information on the performance of the test and provide this information to Roche Molecular Systems, Inc. Roche Molecular Systems, 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 Roche Molecular Systems, Inc. becomes aware.

H. Roche Molecular Systems, Inc., Roche Diagnostics, and other authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized *LightMix® Zika rRT-PCR Test* that is consistent with, and does not exceed, the terms of this letter of authorization.

Roche Molecular Systems, Inc.

I. Roche Molecular Systems, Inc. will notify FDA of any additional authorized distributor(s) of the *LightMix® Zika rRT-PCR Test*, including the name, address, and phone number of any additional, authorized distributor(s).

[8] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that Roche Molecular Systems, Inc., Roche Diagnostics, other authorized distributor(s), 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/).

J. Roche Molecular Systems, Inc. will provide Roche Diagnostics, other authorized distributor(s), and TIB MOLBIOL GmbH with a copy of this EUA, and communicate to Roche Diagnostics, other authorized distributor(s), and TIB MOLBIOL GmbH any subsequent amendments that might be made to this EUA and its authorized accompanying materials (e.g., Fact Sheets, Instructions for Use).

K. Roche Molecular Systems, Inc. may request changes to the authorized *LightMix® Zika rRT-PCR Test* Fact Sheet for Health Care Providers, the authorized *LightMix® Zika rRT-PCR Test* Fact Sheet for Pregnant Women, and the authorized *LightMix® Zika rRT-PCR Test* Fact Sheet for Patients. Such requests will be made by Roche Molecular Systems, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.

L. Roche Molecular Systems, Inc. may request the addition of other instruments for use with the authorized *LightMix® Zika rRT-PCR Test*. Such requests will be made by Roche Molecular Systems, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.

M. Roche Molecular Systems, Inc. may request the addition of other extraction methods for use with the authorized *LightMix® Zika rRT-PCR Test*. Such requests will be made by Roche Molecular Systems, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.

N. Roche Molecular Systems, Inc. may request the addition of other specimen types for use with the authorized *LightMix® Zika rRT-PCR Test*. Such requests will be made by Roche Molecular Systems, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.

O. Roche Molecular Systems, Inc. may request the addition of other control materials for use with the authorized *LightMix® Zika rRT-PCR Test*. Such requests will be made by Roche Molecular Systems, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.

P. Roche Molecular Systems, Inc. may request the addition and/or substitution of other ancillary reagents and materials for use with the authorized *LightMix® Zika rRT-PCR Test*. Such requests will be made by Roche Molecular Systems, Inc. in consultation with, and require concurrence of, DMD/OIR/CDRH.

Q. Roche Molecular Systems, Inc. will assess traceability[9] of the *LightMix® Zika rRT-PCR Test* with FDA-recommended reference material(s). After submission to FDA and DMD/OIR/CDRH's review of and concurrence with the data, Roche Molecular Systems, Inc. will update its labeling to reflect the additional testing.

R. Roche Molecular Systems, Inc., assuming the medical device reporting responsibilities of the manufacturer of the *LightMix® Zika rRT-PCR Test,* will track adverse events and report to FDA under 21 CFR Part 803.

[9] 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 *LightMix® Zika rRT-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 *LightMix® Zika rRT-PCR Test* on the Roche LightCycler® 480 Instrument II, Roche cobas z 480 Analyzer (open channel), or other authorized instruments.

U. Authorized laboratories will perform the *LightMix® Zika rRT-PCR Test* using the automated Roche MagNA Pure 96 System together with the Roche MagNA Pure 96 DNA and Viral NA Large Volume reagent kit, the MagNA Pure Compact Instrument and MagNA Pure Compact Nucleic Acid Isolation Kit I - Large Volume, or other authorized extraction methods.

V. Authorized laboratories will perform the *LightMix® Zika rRT-PCR Test* on human serum, EDTA plasma, 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.[10]

X. Authorized laboratories will collect information on the performance of the test and report to Roche Diagnostics 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 rRT-PCR techniques and use appropriate laboratory and personal protective equipment when handling this kit, and use the test in accordance with the authorized labeling.

Roche Molecular Systems, Inc., Roche Diagnostics, Other Authorized Distributor(s), and Authorized Laboratories

Z. Roche Molecular Systems, Inc., Roche Diagnostics, other 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 *LightMix® Zika rRT-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

[10] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that Roche Molecular Systems, Inc., Roche Diagnostics, other authorized distributor(s), 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/).

requirements set forth in the Act and FDA regulations.

BB. All advertising and promotional descriptive printed matter relating to the use of the authorized *LightMix® Zika rRT-PCR Test* 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.

No advertising or promotional descriptive printed matter relating to the use of the authorized *LightMix® Zika rRT-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 *LightMix® Zika rRT-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