DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

October 10, 2014

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

Dear Dr. Frieden:

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 the Centers for Disease Control and Prevention (CDC) Ebola Virus VP40 Real-time RT-PCR Assay for the presumptive detection of Ebola Zaire virus on a specified instrument in individuals in affected areas with signs and symptoms of Ebola virus infection and/or epidemiological risk factors, by qualified laboratories designated by CDC, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3).

On September 22, 2006, then-Secretary of the Department of Homeland Security (DHS), Michael Chertoff, determined, pursuant to section 319F-2 of the Public Health Service (PHS) Act (42 U.S.C. § 247d-6b), that the Ebola virus presents a material threat against the United States population sufficient to affect national security.[1] 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 declared on August 5, 2014, that circumstances exist justifying the authorization of emergency use of *in vitro* diagnostics for detection of Ebola virus, subject to the terms of any authorization issued under 21 U.S.C. § 360bbb-3(a).[2]

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 CDC Ebola Virus VP40 Real-time RT-PCR Assay (as described in the Scope of Authorization section of this letter (Section II)) in individuals in affected areas with signs and symptoms of Ebola virus infection and/or epidemiological risk factors (as described in the Scope of Authorization section of this letter (Section II)) for the presumptive detection of Ebola Zaire virus by qualified laboratories designated by CDC, subject to the terms of this authorization.

[1] Pursuant to section 564(b)(1) of the Act (21 U.S.C. § 360bbb-3(b)(1)), the HHS Secretary's declaration that supports EUA issuance must be based on one of four determinations, including the identification by the DHS Secretary of a material threat pursuant to section 319F-2 of the PHS Act sufficient to affect national security or the health and security of United States citizens living abroad (section 564(b)(1)(D) of the Act).
[2] U.S. Department of Health and Human Services. *Declaration Regarding Emergency Use of In Vitro Diagnostics for Detection of Ebola Virus*. 79 Fed. Reg. 47141 (August 12, 2014).

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the CDC Ebola Virus VP40 Real-time RT-PCR Assay for the presumptive detection of Ebola Zaire virus 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 Ebola Zaire virus can cause Ebola, a serious or life-threatening disease or condition to humans infected with this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the CDC Ebola Virus VP40 Real-time RT-PCR Assay, when used with the specified instrument, may be effective in diagnosing Ebola Zaire virus, and that the known and potential benefits of the CDC Ebola Virus VP40 Real-time RT-PCR Assay, when used with the specified instrument for diagnosing Ebola Zaire 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 CDC Ebola Virus VP40 Real-time RT-PCR Assay for diagnosing Ebola Zaire virus.[3]

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 CDC Ebola Virus VP40 Real-time RT-PCR Assay by qualified laboratories designated by CDC for the presumptive detection of Ebola Zaire virus in individuals in affected areas with signs and symptoms of Ebola virus infection and/or epidemiological risk factors.

The Authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay:

The CDC Ebola Virus VP40 Real-time RT-PCR Assay is a real-time reverse transcriptase PCR (rRT-PCR) for the *in vitro* qualitative detection of Ebola Zaire virus in whole blood, serum, and plasma specimens from individuals in affected areas with signs and symptoms of Ebola virus infection and/or epidemiological risk factors. The CDC Ebola Virus VP40 Real-time RT-PCR Assay can also be used with urine specimens when tested in conjunction with a patient-matched whole blood, serum, or plasma specimen. The test procedure consists of nucleic acid extraction using only the MagMax Pathogen RNA/DNA kit and the Dynal Bead Retriever followed by rRT-PCR on only the Applied Biosystems (ABI) 7500 Fast Dx Real-Time PCR Instrument.

The CDC Ebola Virus VP40 Real-time RT-PCR Assay consists of two primer/probe sets: VP40 and RP (Rnase P). RNA is extracted from whole blood collected with EDTA as the anticoagulant, plasma, serum, or urine using only the MagMax Pathogen RNA/DNA kit on the Dynal Bead Retriever, not provided with the assay, prior to running on the Applied Biosystems (ABI) 7500 Fast Dx Real-Time PCR Instrument. The resulting purified RNA is analyzed only

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

on the Applied Biosystems (ABI) 7500 Fast Dx Real-Time PCR Instrument using provided primer/probe sets and required reagents with appropriate controls in place.

The CDC Ebola Virus VP40 Real-time RT-PCR Assay includes the following assay controls:

- EBOV VP40 rRT-PCR Positive Control – Used as a control for PCR reagent function.
- NTC – A known negative template control (sterile, nuclease-free water) added during rRT-PCR reaction set-up. Used as a control for PCR reagent function and cross-contamination.
- HSC – A known negative extraction control (human A549 cells) that is **extracted concurrently** with the test samples and included as a sample during rRT-PCR set-up. Should be negative for VP40, but positive for RP. Used as a control to demonstrate successful extraction and as a control for cross-contamination.
- RP – All clinical samples should be tested for human RNAse P gene (using the RP primer and probe set included in the EBOV VP40 rRT-PCR kit) to control for specimen quality and extraction.

The above described CDC Ebola Virus VP40 Real-time RT-PCR Assay, when labeled consistently with the labeling authorized by FDA entitled "Ebola Virus VP40 Real-Time RT-PCR Assay" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), which may be revised by CDC in consultation with FDA, is authorized to be distributed to and used by qualified laboratories designated by CDC under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law.

The above described CDC Ebola Virus VP40 Real-time RT-PCR 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 professionals and patients:

- **Fact Sheet for Health Care Providers: Interpreting CDC Ebola Virus VP40 Real-Time RT-PCR (EBOV VP40 rRT-PCR) Assay Results**

- **Fact Sheet for Patients: Understanding Results from the CDC Ebola Virus VP40 Real-Time RT-PCR (EBOV VP40 rRT-PCR) Assay**

As described in Section IV below, CDC is also authorized to make available additional information relating to the emergency use of the authorized CDC Ebola Virus VP40 Real-time RT-PCR 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 CDC Ebola Virus VP40 Real-time RT-PCR Assay in the specified population, when used for presumptive detection of Ebola Zaire virus, 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 CDC Ebola Virus

VP40 Real-time RT-PCR Assay may be effective in the diagnosis of Ebola Zaire virus infection pursuant to section 564(c)(2)(A) of the Act. The 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 CDC Ebola Virus VP40 Real-time RT-PCR Assay, when used to diagnose Ebola Zaire virus infection in the specified population, meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized CDC Ebola Virus VP40 Real-time RT-PCR 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 DHS's determination described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the CDC Ebola Virus VP40 Real-time RT-PCR Assay described above is authorized to diagnose Ebola Zaire virus infection in individuals in affected areas with signs and symptoms of Ebola virus infection and/or epidemiological risk factors.

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 CDC Ebola Virus VP40 Real-time RT-PCR 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 CDC Ebola Virus VP40 Real-time RT-PCR 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:

Centers for Disease Control and Prevention (CDC)

A. CDC will distribute the authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay with the authorized labeling, as may be revised by CDC in consultation with FDA, only to qualified laboratories designated by CDC.

B. CDC will provide to qualified laboratories designated by CDC the authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay Fact Sheet for Health Care Providers and the authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay Fact Sheet for Patients.

C. CDC will make available on its website the authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay Fact Sheet for Health Care Providers and the authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay Fact Sheet for Patients.

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

E. CDC will ensure that qualified laboratories designated by CDC using the authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay have a process in place for reporting test results to health care professionals and relevant public health authorities, as appropriate.

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, and report to FDA any suspected occurrence of false positive or false negative results of which CDC becomes aware.

I. CDC is authorized to make available additional information relating to the emergency use of the authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay that is consistent with, and does not exceed, the terms of this letter of authorization.

J. CDC may request changes to the authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay Fact Sheet for Health Care Providers or the authorized CDC Ebola Virus VP40 Real-time RT-PCR Assay Fact Sheet for Patients. Such requests will be made by CDC in consultation with FDA.

Qualified Laboratories Designated by CDC

K. Qualified laboratories designated by CDC will include with reports of the results of the CDC Ebola Virus VP40 Real-time RT-PCR Assay the authorized Fact Sheet for Health Care 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.

L. Qualified laboratories designated by CDC will perform the CDC Ebola Virus VP40 Real-time RT-PCR Assay only on the Applied Biosystems (ABI) 7500 Fast Dx Real-Time PCR Instrument.

M. Qualified laboratories designated by CDC will have a process in place for reporting test results to health care professionals and relevant public health authorities, as appropriate.

N. Qualified laboratories designated by CDC will collect information on the performance of the assay, and report to CDC any suspected occurrence of false positive or false negative results of which they become aware.

O. All laboratory personnel using the assay should be appropriately trained in RT-PCR techniques and use appropriate laboratory and personal protective equipment when handling this kit.

CDC and Qualified Laboratories Designated by CDC

P. CDC and qualified laboratories designated by CDC 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

Q. All advertising and promotional descriptive printed matter relating to the use of the authorized CDC Ebola Virus VP40 Real-time RT-PCR 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.

R. All advertising and promotional descriptive printed matter relating to the use of the authorized CDC Ebola Virus VP40 Real-time RT-PCR 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 Emergency Use Authorization for use by qualified laboratories designated by CDC;
- This test has been authorized only for the detection of Ebola Zaire virus 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* diagnostics for detection of Ebola Zaire virus 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 CDC Ebola Virus VP40 Real-time RT-PCR Assay may represent or suggest that this test is safe or effective for the diagnosis of Ebola Zaire virus.

The emergency use of the authorized CDC Ebola Virus VP40 Real-time RT-PCR 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* diagnostics for detection of Ebola virus 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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Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

Enclosures