October 10, 2014

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Dear Dr. Miller:

On August 5, 2014, based on a request by the U.S. Department of Defense (DoD), the Food and Drug Administration (FDA) issued a letter authorizing the emergency use of the DoD *Ebola Zaire (Target 1)* Real-Time PCR (TaqMan®) (EZ1 rRT-PCR) Assay for the presumptive detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014) on specified instruments in individuals in affected areas with signs and symptoms of Ebola virus infection or who are at risk for exposure or may have been exposed to the Ebola Zaire virus (detected in the West Africa outbreak in 2014) in conjunction with epidemiological risk factors, by laboratories designated by DoD, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3).[1] On October 6, 2014, FDA received a request from DoD for an amendment to the Emergency Use Authorization (EUA). In response to that request, and having concluded that revising the August 5, 2014, 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 August 5, 2014, letter authorizing the emergency use of the DoD EZ1 rRT-PCR Assay is being reissued in its entirety with the amendments incorporated.[2]

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.[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 declared on August 5, 2014, that circumstances exist justifying the authorization of emergency

[1] U.S. Food and Drug Administration. *Authorization of Emergency Use of an In Vitro Diagnostic Device for Detection of Ebola Zaire Virus; Availability*. 79 Fed. Reg. 55804 (September 17, 2014).

[2] The amendments to the August 5, 2014, letter authorize the use of the DoD EZ1 rRT-PCR Assay in whole blood or plasma specimens, in addition to Trizol-inactivated whole blood or Trizol-inactivated plasma specimens, from individuals in affected areas with signs and symptoms of Ebola virus infection or who are at risk for exposure or may have been exposed to the Ebola Zaire virus (detected in the West Africa outbreak in 2014) in conjunction with epidemiological risk factors, by laboratories designated by DoD. The amendments also include revisions to the Instructions for Use, product insert, and Fact Sheets for Health Care Providers and Patients to address the addition of whole blood and plasma specimens.

[3] 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).

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).[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 EZ1 rRT-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 or who are at risk for exposure or may have been exposed to the Ebola Zaire virus (detected in the West Africa outbreak in 2014) in conjunction with epidemiological risk factors (as described in the Scope of Authorization section of this letter (Section II)) for the presumptive detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014) by laboratories designated by DoD, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the EZ1 rRT-PCR Assay for the presumptive detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014) 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 (detected in the West Africa outbreak in 2014) can cause Ebola hemorrhagic fever, 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 EZ1 rRT-PCR Assay, when used with the specified instruments, may be effective in diagnosing Ebola Zaire virus (detected in the West Africa outbreak in 2014), and that the known and potential benefits of the EZ1 rRT-PCR Assay, when used with the specified instruments for diagnosing Ebola Zaire virus (detected in the West Africa outbreak in 2014) 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 EZ1 rRT-PCR Assay for diagnosing Ebola Zaire virus (detected in the West Africa outbreak in 2014).[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 EZ1 rRT-PCR Assay by laboratories designated by DoD for the presumptive detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014) in

[4] 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).

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

individuals in affected areas with signs and symptoms of Ebola virus infection or who are at risk for exposure or may have been exposed to the Ebola Zaire virus (detected in the West Africa outbreak in 2014) in conjunction with epidemiological risk factors.

The Authorized EZ1 rRT-PCR Assay:

The EZ1 rRT-PCR Assay is a real-time reverse transcriptase PCR (rRT-PCR) for the *in vitro* qualitative detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014) in whole blood, plasma, Trizol-inactivated whole blood, or Trizol-inactivated plasma specimens from individuals in affected areas with signs and symptoms of Ebola virus infection or who are at risk for exposure or may have been exposed to the Ebola Zaire virus (detected in the West Africa outbreak in 2014) in conjunction with epidemiological risk factors. The test procedure consists of nucleic acid extraction followed by rRT-PCR on only the ABI 7500 FAST DX instrument, the JBAIDS instrument, or the Roche LightCycler instrument.

The EZ1 rRT-PCR Assay consists of two primer/probe sets: EZ1 and RNase P along with the assay master mix and Positive Template Controls (PTC) for each primer/probe set. RNA is extracted from whole blood or Trizol-inactivated whole blood collected with EDTA as the anticoagulant, or plasma or Trizol-inactivated plasma, using the Qiagen QIAamp Viral RNA Mini Kit, purchased separately from the assay, prior to running on an authorized instrument. The QIAamp Viral RNA Mini Kit simplifies purification of viral RNA from the indicated specimens with a fast spin-column procedure. Viral RNA binds specifically to the QIAamp silica membrane, and pure viral RNA is eluted in the buffer provided with the kit. The resulting purified RNA is analyzed on one of the authorized instruments using provided Ebola Zaire and RNase P master mixes with appropriate controls in place.

The EZ1 rRT-PCR Assay includes the following assay controls:

- **RNTC** (Reagents No Template Control) is a negative control used in the amplification step to demonstrate no reagent contamination.
- **SNTC** (Sample Negative Control) is a negative control used in the amplification step to demonstrate no contamination in the sample loading.
- **EZ1 PTC** (Positive Template Control) is a positive control used in the amplification step to confirm target amplification and EZ1 reagent function.
- **RP-PTC** (RNase P Positive Template Control) is a positive control used in the amplification step to ensure the RNase P reagents function.
- **NPC** (Negative Processing Control) is a processing control used during the extraction step to demonstrate that no cross contamination occurred.

The above described EZ1 rRT-PCR Assay, when labeled consistently with the labeling authorized by FDA entitled "*Ebola Zaire (Target 1)* Real-Time PCR (TaqMan®) (EZ1 rRT-PCR) Assay on ABI® 7500 Fast Dx, LightCycler®, and JBAIDS: Instruction Booklet" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), which may be revised by DoD in consultation with FDA, is authorized to be distributed to and used by laboratories designated by DoD under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law.

The above described EZ1 rRT-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 *Ebola Zaire (Target 1)* Real-Time PCR (TaqMan®) (EZ1 rRT-PCR) Assay Results**

- **Fact Sheet for Patients: Understanding Results from the *Ebola Zaire (Target 1)* Real-Time PCR (TaqMan®) (EZ1 rRT-PCR) Test**

As described in Section IV below, DoD is also authorized to make available additional information relating to the emergency use of the authorized EZ1 rRT-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 EZ1 rRT-PCR Assay in the specified population, when used for presumptive detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014), 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 EZ1 rRT-PCR Assay may be effective in the diagnosis of Ebola Zaire virus (detected in the West Africa outbreak in 2014) 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 EZ1 rRT-PCR Assay, when used to diagnose Ebola Zaire virus (detected in the West Africa outbreak in 2014) 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 EZ1 rRT-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 EZ1 rRT-PCR Assay described above is authorized to diagnose Ebola Zaire virus (detected in the West Africa outbreak in 2014) infection in individuals in affected areas with signs and symptoms of Ebola virus infection or who are at risk for exposure or may have been exposed to the Ebola Zaire virus (detected in the West Africa outbreak in 2014) in conjunction with 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 EZ1 rRT-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 EZ1 rRT-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:

U.S. Department of Defense (DoD)

A. DoD will distribute the authorized EZ1 rRT-PCR Assay with the authorized labeling, as may be revised by DoD in consultation with FDA, only to laboratories designated by DoD.

B. DoD will provide to laboratories designated by DoD the authorized EZ1 rRT-PCR Assay Fact Sheet for Health Care Providers and the authorized EZ1 rRT-PCR Assay Fact Sheet for Patients.

C. DoD will make available on its website the authorized EZ1 rRT-PCR Assay Fact Sheet for Health Care Providers and the authorized EZ1 rRT-PCR Assay Fact Sheet for Patients.

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

E. DoD will ensure that laboratories designated by DoD using the authorized EZ1 rRT-PCR Assay have a process in place for reporting test results to health care professionals and relevant public health authorities, as appropriate.

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

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

H. DoD 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 DoD becomes aware.

I. DoD is authorized to make available additional information relating to the emergency use of the authorized EZ1 rRT-PCR Assay that is consistent with, and does not exceed, the terms of this letter of authorization.

J. DoD may request changes to the authorized EZ1 rRT-PCR Assay Fact Sheet for Health Care Providers or the authorized EZ1 rRT-PCR Assay Fact Sheet for Patients. Such requests will be made by DoD in consultation with FDA.

Laboratories Designated by DoD

K. Laboratories designated by DoD will include with reports of the results of the EZ1 rRT-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. Laboratories designated by DoD will perform the EZ1 assay only on the ABI 7500 FAST DX instrument, JBAIDS instrument, or Roche LightCycler instrument.

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

N. Laboratories designated by DoD will collect information on the performance of the assay, and report to DoD 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.

DoD and Laboratories Designated by DoD

P. DoD and laboratories designated by DoD 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 EZ1 rRT-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 EZ1 rRT-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 laboratories designated by DoD;
- This test has been authorized only for the detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014) 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 EZ1 rRT-PCR Assay may represent or suggest that this test is safe or effective for the diagnosis of Ebola Zaire virus (detected in the West Africa outbreak in 2014).

The emergency use of the authorized EZ1 rRT-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