November 26, 2014

Dr. Sven Cramer
Director, Regulatory Affairs
altona Diagnostics GmbH
Mörkenstraße 12
22767 Hamburg
Germany

Dear Dr. Cramer:

On November 10, 2014, based on a request by altona Diagnostics GmbH, the Food and Drug Administration (FDA) issued a letter authorizing the emergency use of the RealStar® Ebolavirus RT-PCR Kit 1.0 for the presumptive detection of RNA from Ebolaviruses[1] on specified instruments in EDTA plasma from individuals with signs and symptoms of Ebola virus infection in conjunction with epidemiological risk factors, by laboratories 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). On November 18, 2014, FDA received a request from altona Diagnostics GmbH for an amendment to the Emergency Use Authorization (EUA). In response to that request, and having concluded that revising the November 10, 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 November 10, 2014, letter authorizing the emergency use of the RealStar® Ebolavirus RT-PCR Kit 1.0 is being reissued in its entirety with the amendments incorporated.[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.[4] Pursuant to section 564(b)(1) of the Act

[1] This authorization is being issued in response to the epidemic in West Africa involving Zaire ebolavirus. This assay is intended for the qualitative detection of RNA from Ebolaviruses (such as Zaire ebolavirus [including the Zaire ebolavirus strain detected in the West Africa outbreak 2014], Sudan ebolavirus, Tai Forest ebolavirus, Bundibugyo ebolavirus, and Reston ebolavirus); however, it does not distinguish between the different Ebola virus species or strains.

[2] For ease of reference, this letter will refer to this type of laboratory as "CLIA High Complexity Laboratories."

[3] The amendments to the November 10, 2014, letter allow, in addition to altona Diagnostics GmbH, distributors that are authorized by altona Diagnostics GmbH to distribute the RealStar® Ebolavirus RT-PCR Kit 1.0 with certain conditions applicable to such authorized distributor(s). Because this assay may be distributed outside the U.S., the amendments also allow the use of this assay under this EUA, with certain conditions, at non-U.S. laboratories that are similarly qualified as CLIA High Complexity Laboratories. The Instructions for Use and Fact Sheet for Health Care Providers have also been updated to incorporate these amendments.

[4] 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

(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).[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 RealStar® Ebolavirus RT-PCR Kit 1.0 (as described in the Scope of Authorization section of this letter (Section II)) in individuals with signs and symptoms of Ebola virus infection in conjunction with epidemiological risk factors (as described in the Scope of Authorization section of this letter (Section II)) for the presumptive detection of RNA from Ebolaviruses by CLIA High Complexity Laboratories, or similarly qualified non-U.S. laboratories, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the RealStar® Ebolavirus RT-PCR Kit 1.0 for the presumptive detection of RNA from Ebolaviruses 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. Ebolaviruses can cause Ebola virus disease, 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 RealStar® Ebolavirus RT-PCR Kit 1.0, when used with the specified instruments, may be effective in diagnosing Ebolavirus infection, and that the known and potential benefits of the RealStar® Ebolavirus RT-PCR Kit 1.0, when used with the specified instruments for diagnosing Ebolavirus 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 RealStar® Ebolavirus RT-PCR Kit 1.0 for diagnosing Ebolavirus 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 RealStar® Ebolavirus RT-PCR Kit 1.0 by CLIA High Complexity Laboratories, or similarly qualified non-U.S. laboratories, for the presumptive detection of RNA from Ebolaviruses in individuals with signs and symptoms of Ebola virus infection in conjunction with epidemiological risk factors.

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).

[5] 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).

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

The Authorized RealStar® Ebolavirus RT-PCR Kit 1.0:

The RealStar® Ebolavirus RT-PCR Kit 1.0 is a reverse transcriptase Polymerase Chain Reaction (RT-PCR) system for the *in vitro* qualitative detection of RNA from Ebolaviruses in human EDTA plasma specimens from individuals with signs and symptoms of Ebola virus infection in conjunction with epidemiological risk factors. RNA is extracted from whole blood collected with EDTA as the anticoagulant using only the QIAamp Viral RNA Mini Kit. The test procedure consists of three processes in a single tube assay: reverse transcription of target RNA and Internal Control RNA to cDNA, PCR amplification of target and Internal Control cDNA, and simultaneous detection of PCR amplicons by fluorescent dye labelled probes to analyze samples for the presence of RNA from Ebola viruses on only the ABI Prism® 7500 SDS instrument, the ABI Prism® 7500 Fast SDS instrument, the LightCycler® 480 Instrument II, and the CFX96™ system/Dx real-time system.

The assay is designed to detect all Ebolavirus species. The reagent system includes a heterologous amplification system (Internal Control) to identify possible RT-PCR inhibition and to confirm the integrity of the reagents of the kit.

The RealStar® Ebolavirus RT-PCR Kit 1.0 includes the following assay control:

> The **Internal Control** contains a defined copy number of an "artificial" RNA molecule with no homologies to any other known sequences. It has to be added to the nucleic acid extraction procedure and is reverse transcribed, amplified and detected in parallel to the Ebolavirus specific RNA. The function of the Internal Control is to ensure the integrity of Ebolavirus specific real-time RT-PCR results by indicating potential RT-PCR inhibition.
>
> The **PCR grade water** is to be used as negative control for the RT-PCR reaction. Its function is to indicate contamination of RT-PCR reagents.
>
> The "**Positive Control Target EBOLA**" consists of an *in vitro* transcript which contains the target sequence used by the RealStar® Ebolavirus RT-PCR Kit 1.0 for the detection of Ebolavirus specific RNA. The "Positive Control Target EBOLA" is used as positive control for the RT-PCR and verifies the functionality of the Ebolavirus RNA specific RT-PCR detection system, which is included in the RealStar® Ebolavirus RT-PCR Kit 1.0.

The above described RealStar® Ebolavirus RT-PCR Kit 1.0, when labeled consistently with the labeling authorized by FDA entitled "RealStar® Ebolavirus RT-PCR Kit 1.0 Instructions for Use" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#ebola), which may be revised only by altona Diagnostics GmbH in consultation with FDA, is authorized to be distributed to and used by CLIA High Complexity Laboratories, or similarly qualified non-U.S. laboratories, under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law.

The above described RealStar® Ebolavirus RT-PCR Kit 1.0 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 RealStar® Ebolavirus RT-PCR Kit 1.0 Results**

- **Fact Sheet for Patients: Understanding Results from the RealStar® Ebolavirus RT-PCR Kit 1.0**

As described in Section IV below, altona Diagnostics GmbH and its authorized distributor(s) are also authorized to make available additional information relating to the emergency use of the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 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 RealStar® Ebolavirus RT-PCR Kit 1.0 test in the specified population, when used for presumptive detection of RNA from Ebolaviruses 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 RealStar® Ebolavirus RT-PCR Kit 1.0 may be effective in the diagnosis of infection with Ebolaviruses 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 RealStar® Ebolavirus RT-PCR Kit 1.0, when used to diagnose infection with Ebolaviruses 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 RealStar® Ebolavirus RT-PCR Kit 1.0 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 RealStar® Ebolavirus RT-PCR Kit 1.0 described above is authorized to diagnose infection with Ebolaviruses in individuals with signs and symptoms of Ebola virus infection 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 RealStar® Ebolavirus RT-PCR Kit 1.0 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 RealStar® Ebolavirus RT-PCR Kit 1.0.

- 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:

altona Diagnostics GmbH and Its Authorized Distributor(s)

A. altona Diagnostics GmbH and its authorized distributor(s) will distribute the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 with the authorized labeling, as may be revised only by altona Diagnostics GmbH in consultation with FDA, only to CLIA High Complexity Laboratories or similarly qualified non-U.S. laboratories.

B. altona Diagnostics GmbH and its authorized distributor(s) will provide to CLIA High Complexity Laboratories or similarly qualified non-U.S. laboratories the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 Fact Sheet for Health Care Providers and the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 Fact Sheet for Patients.

C. altona Diagnostics GmbH and its authorized distributor(s) will make available on their websites the RealStar® Ebolavirus RT-PCR Kit 1.0 test Fact Sheet for Health Care Providers and the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 Fact Sheet for Patients.

D. altona Diagnostics GmbH and its authorized distributor(s) will inform CLIA High Complexity Laboratories or similarly qualified non-U.S. laboratories and relevant public health authority(ies) of this EUA, including the terms and conditions herein.

E. altona Diagnostics GmbH and its authorized distributor(s) will ensure that CLIA High Complexity Laboratories or similarly qualified non-U.S. laboratories using the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 have a process in place for reporting test results to health care professionals and relevant public health authorities, as appropriate.

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

G. altona Diagnostics GmbH and its authorized distributor(s) 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 altona Diagnostics GmbH and its authorized distributor(s) become aware.

H. altona Diagnostics GmbH and its authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 that is consistent with, and does not exceed, the terms of this letter of authorization.

altona Diagnostics GmbH

I. altona Diagnostics GmbH 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).

J. altona Diagnostics GmbH only may request changes to the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 Fact Sheet for Health Care Providers or the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 Fact Sheet for Patients. Such requests will be made only by altona Diagnostics GmbH in consultation with FDA.

K. altona Diagnostics GmbH will track adverse events and report to FDA under 21 CFR Part 803.

CLIA High Complexity Laboratories and Similarly Qualified Non-U.S. Laboratories

L. CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories will include with reports of the results of the RealStar® Ebolavirus RT-PCR Kit 1.0 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.

M. CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories will perform the RealStar® Ebolavirus RT-PCR Kit 1.0 on only the ABI Prism® 7500 SDS instrument, the ABI Prism® 7500 Fast SDS instrument, the LightCycler® 480 Instrument II, and the CFX96™ system/Dx real-time system.

N. CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories will have a process in place for reporting test results to health care professionals and relevant public health authorities, as appropriate.

O. CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories will collect information on the performance of the assay, and report to altona Diagnostics GmbH and its authorized distributor(s) any suspected occurrence of false positive or false negative results of which they become aware.

P. All laboratory personnel using the assay should be appropriately trained in RealStar® Ebolavirus RT-PCR Kit 1.0 on the specified instruments and use appropriate laboratory and personal protective equipment when handling this kit.

altona Diagnostics GmbH, Its Authorized Distributor(s), CLIA High Complexity Laboratories, and Similarly Qualified Non-U.S. Laboratories

Q. altona Diagnostics GmbH, its authorized distributor(s), CLIA High Complexity Laboratories, and similarly qualified non-U.S. 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

R. All advertising and promotional descriptive printed matter relating to the use of the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 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.

S. All advertising and promotional descriptive printed matter relating to the use of the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 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 CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories;
- This test has been authorized only for the detection of RNA from Ebolaviruses (such as Zaire ebolavirus, [including the Zaire ebolavirus strain detected in the West Africa outbreak 2014], Sudan ebolavirus, Tai Forest ebolavirus, Bundibugyo ebolavirus, and Reston ebolavirus) 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 RealStar® Ebolavirus RT-PCR Kit 1.0 may represent or suggest that this test is safe or effective for the diagnosis of infection with Ebolavirus.

The emergency use of the authorized RealStar® Ebolavirus RT-PCR Kit 1.0 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