DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

February 12, 2016

Dr. Sven Cramer
Head of Regulatory Affairs
altona Diagnostics GmbH
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22767 Hamburg
Germany

Dear Dr. Cramer:

On July 17, 2015, based on a request by altona Diagnostics GmbH, the Food and Drug Administration (FDA) issued a letter authorizing the emergency use of the RealStar® MERS-CoV RT-PCR Kit U.S. for the *in vitro* qualitative detection of RNA from the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), formerly known as Novel Coronavirus 2012 or NCV-2012, in lower respiratory specimens (tracheal aspirate/tracheal secretions) from individuals with signs and symptoms of infection with MERS-CoV in conjunction with epidemiological risk factors for the presumptive detection of MERS-CoV, by laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high complexity tests,[1] and 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).[2] On January 5, 2016, altona Diagnostics GmbH submitted a request for an amendment to the Emergency Use Authorization (EUA). In response to that request, and having concluded that revising the July 17, 2015, 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 July 17, 2015, letter authorizing the emergency use of the RealStar® MERS-CoV RT-PCR Kit U.S. is being reissued in its entirety with the amendments incorporated.[3]

On May 29, 2013, 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 United States citizens living abroad, and that involves MERS-CoV.[4]

[1] For ease of reference, this letter will refer to this type of laboratory as "CLIA High Complexity Laboratories."
[2] U.S. Food and Drug Administration. *Authorization of Emergency Use of an In Vitro Diagnostic for Detection of Middle East Respiratory Syndrome Coronavirus; Availability.* 80 Fed. Reg. 52757 (September 1, 2015).
[3] The amendments to the July 17, 2015, letter authorize the expanded use of the RealStar® MERS-CoV RT-PCR Kit U.S. to include the *in vitro* qualitative detection of genomic RNA from MERS-CoV in nasopharyngeal swabs from asymptomatic individuals suspected of exposure to MERS-CoV based on epidemiological risk factors (e.g., contact with a probable or confirmed MERS-CoV case, history of travel to geographic locations where MERS-CoV cases were detected, or other epidemiologic links for which MERS-CoV testing may be indicated.) The amendments also include a new Fact Sheet for Asymptomatic Individuals Suspected of Exposure to MERS-CoV Cases and revisions to the Instructions for Use, and Fact Sheets for Health Care Providers and Patients.
[4] 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.

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* diagnostics for the detection of MERS-CoV, subject to the terms of any authorization issued under section 564(a) of the Act (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 RealStar® MERS-CoV RT-PCR Kit U.S. (as described in the Scope of Authorization section of this letter (Section II)) for the presumptive detection of MERS-CoV in individuals meeting MERS-CoV clinical (signs and symptoms associated with MERS-CoV infection) and/or epidemiological criteria (e.g., contact with a probable or confirmed MERS-CoV case, history of travel to geographic locations where MERS-CoV cases were detected, or other epidemiologic links for which MERS-CoV testing may be indicated) for the presumptive detection of MERS-CoV by CLIA High Complexity Laboratories and 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® MERS-CoV RT-PCR Kit U.S. for the presumptive detection of MERS-CoV 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. MERS-CoV can cause a serious or life threatening disease or condition, including severe respiratory illness, 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® MERS-CoV RT-PCR Kit U.S. when used with the specified instruments may be effective in diagnosing MERS-CoV infection, and that the known and potential benefits of the RealStar® MERS-CoV RT-PCR Kit U.S., when used for diagnosing MERS-CoV 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® MERS-CoV RT-PCR Kit U.S. for diagnosing MERS-CoV.[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® MERS-CoV RT-PCR Kit U.S. by CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories for the *in vitro* qualitative detection of RNA from MERS-CoV in individuals meeting MERS-CoV clinical (signs and symptoms associated with MERS-CoV infection) and/or epidemiological criteria (e.g., contact with a probable or confirmed MERS-CoV case, history of travel to geographic locations where

[5] U.S. Department of Health and Human Services. *Determination and Declaration Regarding Emergency Use of In Vitro Diagnostics for Detection of Middle East Respiratory Syndrome Coronavirus (MERS-CoV)*. 78 Fed. Reg. 33842 (June 5, 2013).

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

MERS-CoV cases were detected, or other epidemiologic links for which MERS-CoV testing may be indicated) for the presumptive detection of MERS-CoV.

The Authorized RealStar® MERS-CoV RT-PCR Kit U.S.

The RealStar® MERS-CoV RT-PCR Kit U.S. is a real-time reverse transcriptase polymerase chain reaction (rRT-PCR) for the *in vitro* qualitative detection of RNA from MERS-CoV (1) in lower respiratory specimens (tracheal aspirate/tracheal secretions) or any other authorized specimens from individuals with signs and symptoms of infection with MERS-CoV in conjunction with epidemiological risk factors; and (2) nasopharyngeal swabs or any other authorized specimens from asymptomatic individuals suspected of exposure to MERS-CoV cases based on epidemiological risk factors (e.g., contact with a probable or confirmed MERS-CoV case, history of travel to geographic locations where MERS-CoV cases were detected, or other epidemiologic links for which MERS-CoV testing may be indicated) for the presumptive detection of MERS Co-V.

The test procedure consists of nucleic acid extraction using the QIAamp® Viral RNA Mini Kit, or other authorized extraction methods followed by rRT-PCR on Applied Biosystems PCR instrument systems (i.e., ABI Prism® 7500 SDS, ABI Prism® 7500 Fast SDS), Roche LightCycler® 480 Instrument II, BIO-RAD PCR instrument system (i.e., CFX96™ system/Dx real-time system, CFX96 Touch™ Deep Well Real-Time PCR Detection System), Corbett Research Rotor-Gene® 6000, QUIAGEN Rotor-Gene® Q5/6 plex/MDx Platform, and Siemens VERSANT® kPCR Molecular System AD, or other authorized instruments.

The RealStar® MERS-CoV RT-PCR Kit U.S. consists of two independent assays, one targeting a region upstream of the E gene (*upE*) and the other targeting open reading frame 1a (*orf1a*) of the MERS-CoV genome. Both assays include a heterologous amplification system (Internal Control) to identify possible RT-PCR inhibition and to confirm the integrity of the reagents of the kit.

The test is based on rRT-PCR technology, utilizing reverse transcriptase (RT) reaction to convert RNA into complementary DNA (cDNA), polymerase chain reaction (PCR) for the amplification of specific target sequences, and target specific probes for the detection of the amplified DNA. The probes are labeled with fluorescent reporter and quencher dyes. In both assays, probes specific for MERS-CoV RNA are labeled with the fluorophore FAM (amine-reactive succinimidyl esters of carboxyfluorescein).

The RealStar® MERS-CoV RT-PCR Kit U.S. uses the following primer and probe sets:

a) Detection of MERS-CoV *orf1a*:
- Forward primer: P1358
- Reverse primer: P1359
- Probe: S653

b) Detection of MERS-CoV *upE*:
- Forward primer: P1356
- Reverse primer: P1357
- Probe: S652

c) Detection of the Internal Control:
- Forward primer: P30
- Reverse primer: P31
- Probe: S116

Control material to be used with the RealStar® MERS-CoV RT-PCR Kit U.S. test includes:

a) Internal 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 MERS-CoV specific RNA. The function of the Internal Control is to ensure the integrity of MERS-CoV specific rRT-PCR results by indicating potential RT-PCR inhibition.

b) PCR grade water

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.

c) Positive Control

The Positive Control consists of dilutions of a 1:1 mixture of two *in vitro* transcripts (IVT). One IVT with a length of 590 nucleotides (nt) contains a sequence (399 nt) of open reading frame 1a of MERS-CoV, whereas the other IVT with a length of 590 nt contains a sequence (399 nt) upstream of the E gene of the MERS-CoV genome. The *orf1a* specific IVT as well as the *upE* specific IVT contain the target region for the *orf1a* and the *upE* specific detection system, respectively (399 nt in length for *orf1a* and 399 nt in length for *upE*) which is used to detect MERS-CoV specific RNA with the RealStar® MERS-CoV RT-PCR Kit U.S. The Positive Control is used for the RT-PCR to verify the functionality of the MERS-CoV RNA specific RT-PCR detection system, which is included in the RealStar® MERS-CoV RT-PCR Kit U.S.

The above described RealStar® MERS-CoV RT-PCR Kit U.S., when labeled consistently with the labeling authorized by FDA, entitled "RealStar® MERS-CoV RT-PCR Kit U.S. Instructions for Use" (available at www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm, which may be revised only with written permission of FDA, is authorized to be distributed to and used by CLIA High Complexity Laboratories and 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® MERS-CoV RT-PCR Kit U.S. 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 and patients:

- Fact Sheet for Health Care Providers: Interpreting RealStar® MERS-CoV RT-PCR Kit U.S. Test Results

- Fact Sheet for Patients: Understanding Results from the RealStar® MERS-CoV RT-PCR Kit U.S.

- Fact Sheet for Asymptomatic Individuals Suspected of Exposure to MERS-CoV Cases: Understanding Results from the RealStar® MERS-CoV RT-PCR Kit U.S.

As described in section IV below, altona Diagnostics GmbH and any authorized distributor(s) are also authorized to make available additional information relating to the emergency use of the authorized RealStar® MERS-CoV RT-PCR Kit U.S. 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® MERS-CoV RT-PCR Kit U.S. in the specified population, when used for presumptive detection of MERS-CoV, 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® MERS-CoV RT-PCR Kit U.S. may be effective in the diagnosis of MERS-CoV infection pursuant to section 564(c)(2)(A) of the Act. FDA has reviewed the scientific information available including the information supporting the conclusions described in Section I above, and concludes that the authorized RealStar® MERS-CoV RT-PCR Kit U.S., when used to diagnose MERS-CoV infection in the specified populations in conjunction with epidemiological risk factors, meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized RealStar® MERS-CoV RT-PCR Kit U.S. 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 under section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the RealStar® MERS-CoV RT-PCR Kit U.S. described above is authorized to diagnose MERS-CoV infection in individuals meeting MERS-CoV clinical (signs and symptoms associated with MERS-CoV infection) and/or epidemiological criteria (e.g., contact with a probable or confirmed MERS-CoV case, history of travel to geographic locations where MERS-CoV cases were detected, or other epidemiologic links for which MERS-CoV testing may be indicated)

This EUA will cease to be effective when the declaration of emergency 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® MERS-CoV RT-PCR Kit U.S. 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® MERS-CoV RT-PCR Kit U.S.

- Labeling requirements for cleared, approved, or investigational devices, including labeling requirements under 21 CFR 809.10 and 809.30, except for the intended use statement (21 CFR 809.10(a)(2), (b)(2)), adequate directions for use (section 502(f) of the Act (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 Any Authorized Distributor(s)

A. altona Diagnostics GmbH and any authorized distributor(s) will distribute the authorized RealStar® MERS-CoV RT-PCR Kit U.S. with the authorized labeling, as may be revised with written permission of FDA, only to CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories.

B. altona Diagnostics GmbH and any authorized distributor(s) will provide to CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Health Care Providers, the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Patients, and the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Asymptomatic Individuals Suspected of Exposure to MERS-CoV Cases.

C. altona Diagnostics GmbH and any authorized distributor(s) will make available on their websites the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Health Care Providers, the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Patients, and the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Asymptomatic Individuals Suspected of Exposure to MERS-CoV Cases.

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

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

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

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

altona Diagnostics GmbH

I. altona Diagnostics GmbH will notify FDA of any authorized distributor(s) of the RealStar® MERS-CoV RT-PCR Kit U.S., including the name, address, and phone number of any authorized distributor(s).

J. altona Diagnostics GmbH will provide any authorized distributor(s) with a copy of this EUA, and communicate to any 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. altona Diagnostics GmbH only may request changes to the RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Health Care Providers, the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Patients, or the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Asymptomatic Individuals Suspected of Exposure to MERS-CoV Cases. Such requests will be made only by altona Diagnostics GmbH in consultation with FDA.

L. altona Diagnostics GmbH may request the addition of other specimen types for use with the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Such requests will be made by altona Diagnostics GmbH in consultation with, and require concurrence of FDA.

M. altona Diagnostics GmbH may request the addition of other extraction methods for use with the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Such requests will be made by altona Diagnostics GmbH in consultation with, and require concurrence of FDA.

N. altona Diagnostics GmbH may request the addition of other real-time PCR instruments for use with the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Such requests will be made by altona Diagnostics GmbH in consultation with, and require concurrence of FDA.

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

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

P. CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories will include with reports of the results of the RealStar® MERS-CoV RT-PCR Kit U.S. the Fact Sheet for Health Care Providers, the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Patients, and the authorized RealStar® MERS-CoV RT-PCR Kit U.S. Fact Sheet for Asymptomatic Individuals Suspected of Exposure to MERS-CoV Cases.

Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.

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

R. 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 any authorized distributor(s) any suspected occurrence of false positive or false negative results of which the laboratories become aware.

S. All laboratory personnel using the assay will be appropriately trained on the use of the RealStar® MERS-CoV RT-PCR Kit U.S. on the specified instrument systems or other authorized instruments and use appropriate laboratory and personal protective equipment when handling this test.

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

T. altona Diagnostics GmbH, any 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

U. All advertising and promotional descriptive printed matter relating to the use of the authorized RealStar® MERS-CoV RT-PCR Kit U.S. will 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.

V. All advertising and promotional descriptive printed matter relating to the use of the authorized RealStar® MERS-CoV RT-PCR Kit U.S. will 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 CLIA High Complexity Laboratories and similarly qualified non-U.S. laboratories;
- This test has been authorized only for the detection of MERS-CoV; 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 MERS-CoV 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® MERS-CoV RT-PCR Kit U.S. may represent or suggest that this test is safe or effective for the diagnosis of MERS-CoV infection.

The emergency use of the authorized RealStar® MERS-CoV RT-PCR Kit U.S.
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 MERS-CoV is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

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Stephen M. Ostroff, M.D.
Acting Commissioner of Food and Drugs

Enclosures