March 23, 2015

James F. Kelly, Ph.D.
Executive Director, Regulatory Affairs
Cepheid
904 Caribbean Drive
Sunnyvale, CA 94089

Dear Dr. Kelly:

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 Xpert® Ebola Assay for the presumptive detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014) on the GeneXpert Instrument Systems in EDTA venous whole blood specimens 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 moderate complexity tests and by laboratories certified under CLIA to perform high complexity tests,[1] or in similarly qualified non-U.S. laboratories, by clinical laboratory personnel who have received specific training on the use of the Xpert® Ebola Assay on GeneXpert Instrument Systems, 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.[2] 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 the Department of Health and Human Services (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).[3]

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 Xpert® Ebola Assay (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

[1] For ease of reference, this letter will refer to these two types of laboratories together as "CLIA Moderate and High Complexity Laboratories."
[2] 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).
[3] 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).

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).

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the Xpert® Ebola 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 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 Xpert® Ebola Assay may be effective in diagnosing Ebola Zaire virus (detected in the West Africa outbreak in 2014) infection, and that the known and potential benefits of the Xpert® Ebola Assay 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 Xpert® Ebola Assay for diagnosing Ebola Zaire virus (detected in the West Africa outbreak in 2014) infection.[4]

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 Xpert® Ebola Assay in CLIA Moderate and High Complexity Laboratories or in similarly qualified non-U.S. laboratories for the presumptive detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014) in individuals with signs and symptoms of Ebola virus infection in conjunction with epidemiological risk factors.

The Authorized Xpert® Ebola Assay

The Xpert® Ebola Assay is an automated test intended for the *in vitro* qualitative detection of Ebola Zaire virus RNA from EDTA venous whole blood specimens. The assay is performed on the Cepheid GeneXpert Instrument Systems. GeneXpert Instrument Systems automate and integrate sample preparation, nucleic acid extraction, amplification, and detection of the target sequence in simple or complex samples using real-time reverse transcriptase PCR (rRT-PCR). The systems consist of an instrument, personal computer, and preloaded software for running tests and viewing the results. The test is run in single-use disposable GeneXpert cartridges that hold the sample extraction and rRT-PCR reagents and run the sample preparation and rRT-PCR processes. Because the cartridges are self-contained, cross-contamination between samples is minimized. End users collect the sample, transfer it to a sample transport tube containing a

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

buffer that inactivates virus, and transfer the inactivated virus sample to the cartridge. All subsequent steps of sample extraction, amplification, and detection are fully automated.

Each Xpert® Ebola Assay includes a Sample Adequacy Control (SAC), Sample Processing Control (SPC), and Probe Check Control (PCC):

- Sample Adequacy Control (SAC): Ensures that the sample was correctly added to the cartridge. The SAC verifies that the correct volume of sample has been added in the sample chamber. The SAC passes if it meets the validated acceptance criteria.

- Sample Processing Control (SPC): Ensures the sample was correctly processed. The SPC is an Armored RNA® in the form of a dry bead that is included in each cartridge to verify adequate processing of the sample virus. The SPC verifies that lysis of Ebola has occurred if the organism is present and verifies that the specimen processing is adequate. Additionally this control detects specimen-associated inhibition of the RT-PCR reaction. The SPC should be positive in a negative sample and can be negative or positive in a positive sample. The SPC passes if it meets the validated acceptance criteria. The SPC is also referred to as the Cepheid Internal Control (CIC).

- Probe Check Control (PCC): Before the start of the PCR reaction, the GeneXpert Instrument System measures the fluorescence signal from the probes to monitor bead rehydration, reaction tube filling, probe integrity, and dye stability. There are two probe check controls. The first PCC occurs after sample processing but before the start of the RT-PCR reaction and the second PCC occurs before the PCR reaction starts. The PCCs pass if they meet the validated acceptance criteria.

The above described Xpert® Ebola Assay, when labeled consistently with the labeling authorized by FDA entitled "Xpert® Ebola Assay Instructions for Use" (available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), which may be revised by Cepheid in consultation with FDA, is authorized to be distributed to and used by CLIA Moderate and High Complexity Laboratories and similarly qualified non-U.S. laboratories, despite the fact that it does not meet certain requirements otherwise required by federal law.

The above described Xpert® Ebola 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 Xpert® Ebola Assay Results

- Fact Sheet for Patients: Understanding Results from the Cepheid® Xpert® Ebola Assay

As described in section IV below, Cepheid and any authorized distributor(s) are also authorized to make available additional information relating to the emergency use of the authorized Xpert® Ebola 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 Xpert® Ebola 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 Xpert® Ebola 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. 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 Xpert® Ebola 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 Xpert® Ebola 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 Xpert® Ebola Assay described above is authorized to diagnose Ebola Zaire virus (detected in the West Africa outbreak in 2014) infection 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 Xpert® Ebola 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 Xpert® Ebola 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:

Cepheid and Any Authorized Distributor(s)

A. Cepheid and any authorized distributor(s) will distribute the authorized Xpert® Ebola Assay with the authorized labeling, as may be revised only by Cepheid in consultation with FDA, to CLIA Moderate and High Complexity Laboratories or similarly qualified non-U.S. laboratories.

B. Cepheid and any authorized distributor(s) will provide to CLIA Moderate and High Complexity Laboratories or similarly qualified non-U.S. laboratories the authorized Xpert® Ebola Assay Fact Sheet for Health Care Providers and the authorized Xpert® Ebola Assay Fact Sheet for Patients.

C. Cepheid and any authorized distributor(s) will make available on their websites the Xpert® Ebola Assay Fact Sheet for Health Care Providers and the authorized Xpert® Ebola Assay Fact Sheet for Patients.

D. Cepheid and any authorized distributor(s) will inform CLIA Moderate and 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. Cepheid and any authorized distributor(s) will ensure that CLIA Moderate and High Complexity Laboratories or similarly qualified non-U.S. laboratories using the authorized Xpert® Ebola Assay 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, Cepheid and any authorized distributor(s) will maintain records of device usage.

G. Cepheid 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 Cepheid and any authorized distributor(s) become aware.

H. Cepheid and any authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized Xpert® Ebola Assay that is consistent with, and does not exceed, the terms of this letter of authorization.

Cepheid

I. Cepheid will notify FDA of any authorized distributor(s) of the Xpert® Ebola Assay, including the name, address, and phone number of any authorized distributor(s).

J. Cepheid 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. Cepheid only may request changes to the authorized Xpert® Ebola Assay Fact Sheet for Health Care Providers or the authorized Xpert® Ebola Assay Fact Sheet for Patients. Such requests will be made only by Cepheid in consultation with FDA.

L. Cepheid may request the addition of other specimen types for use with the authorized Xpert® Ebola Assay. Such requests will be made by Cepheid in consultation with, and require concurrence of, FDA.

M. Cepheid will track adverse events and report to FDA under 21 CFR part 803.

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

N. CLIA Moderate and High Complexity Laboratories or similarly qualified non-U.S. laboratories will include with reports of the results of the Xpert® Ebola 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.

O. CLIA Moderate and High Complexity Laboratories or 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.

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

Q. All laboratory personnel using the assay will be appropriately trained on the use of the Xpert® Ebola Assay on GeneXpert Instrument Systems and use appropriate laboratory and personal protective equipment when handling this kit.

Cepheid, Any Authorized Distributors, and CLIA Moderate and High Complexity Laboratories or Similarly Qualified Non-U.S. Laboratories

R. Cepheid, any authorized distributor(s), and CLIA Moderate and High Complexity Laboratories or 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

S. All advertising and promotional descriptive printed matter relating to the use of the authorized Xpert® Ebola 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.

T. All advertising and promotional descriptive printed matter relating to the use of the authorized Xpert® Ebola 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 EUA for use by CLIA Moderate and High Complexity Laboratories or similarly qualified non-U.S. laboratories;
- This test has been authorized only for the detection of Ebola Zaire virus (detected in the West Africa outbreak in 2014); 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 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 Xpert® Ebola 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 Xpert® Ebola Assay 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

Enclosure