

May 12, 2015

Thomas R. Frieden, M.D., M.P.H.
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's (CDC) Enterovirus D68 2014 Real-time RT-PCR Assay (EV-D68 2014 rRT-PCR) for the *in vitro* qualitative detection of RNA from the enterovirus D68 (EV-D68) strains detected in North America in 2014 in upper respiratory specimens (such as nasopharyngeal (NP) swabs, oropharyngeal (OP) swabs, dual NP/OP swabs, and/or nasal washes) and sera in conjunction with patient-matched upper respiratory specimen(s) from individuals with signs and symptoms of EV-D68 infection and/or epidemiologic risk factors, by qualified laboratories designated by CDC on specified instruments, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3).

On February 6, 2015, 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 EV-D68.¹ 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 then declared that circumstances exist justifying the authorization of the emergency use of *in vitro* diagnostics for the detection of EV-D68, 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 EV-D68 2014 rRT-PCR (as described in the Scope of Authorization section of this letter (section II)) in individuals with signs and symptoms of EV-D68 infection and/or epidemiologic risk factors (as described in the Scope of Authorization section of this letter (section II)) for the *in vitro* qualitative detection of EV-D68 strains detected in North America in 2014.

¹ 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.

² HHS. *Determination and Declaration Regarding Emergency Use of New In Vitro Diagnostics for Detection of Enterovirus D68*. 80 Fed. Reg. 10685 (February 27, 2015).

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the EV-D68 2014 rRT-PCR for the *in vitro* qualitative detection of EV-D68 strains detected in North America 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. EV-D68 can cause EV-D68 infection, 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 EV-D68 2014 rRT-PCR, when used with the specified instruments, may be effective in diagnosing EV-D68 infection, and that the known and potential benefits of the EV-D68 2014 rRT-PCR for diagnosing EV-D68 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 EV-D68 2014 rRT-PCR for diagnosing EV-D68 infection.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 EV-D68 2014 rRT-PCR by qualified laboratories designated by CDC for the *in vitro* qualitative detection of EV-D68 strains detected in North America in 2014 in individuals with signs and symptoms of EV-D68 infection and/or epidemiologic risk factors.

The Authorized Enterovirus D68 2014 Real-time RT-PCR Assay

The EV-D68 2014 rRT-PCR is a real-time reverse transcriptase PCR (rRT-PCR) for the *in vitro* qualitative detection of EV-D68 strains detected in North America in 2014 in upper respiratory specimens (such as NP swabs, OP swabs, dual NP/OP swabs, and/or nasal washes), sera in conjunction with patient-matched upper respiratory specimen(s), and other authorized specimen types from individuals with signs and symptoms of EV-D68 infection and/or epidemiologic risk factors. The test procedure consists of nucleic acid extraction using the QIAamp Viral RNA Mini Kit, QIAamp DSP Viral RNA Mini Kit, bioMérieux easyMAG, or other authorized extraction methods, followed by rRT-PCR on Applied Biosystems PCR instrument systems (i.e., AB 7500, AB 7500 Fast, and AB 7500 Fast Dx Real-Time PCR Systems with SDS software) or other authorized instruments.

The EV-D68 2014 rRT-PCR is based on one-step real-time reverse transcription polymerase chain reaction. The Assay employs one primer and probe set (VP1.2014) that targets the viral protein 1 (VP1) gene of the EV-D68 genome, and one primer and probe set (RP) that targets the human RNase P gene.

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

The EV-D68 2014 rRT-PCR uses the following primer/probe sets:

VP1.2014: targets the EV-D68 viral protein 1 (VP1) gene

RP^a: targets the human Ribonuclease P gene. This primer and probe set is included as a control for specimen quality, to confirm that human nucleic acid was successfully extracted from the clinical specimen.

The EV-D68 2014 rRT-PCR includes the following assay controls:

1. EV-D68 2014 rRT-PCR Positive Control is comprised of synthetic, *in vitro* transcribed single-stranded, positive-sense RNA transcript.
2. RNase P Primer and Probe Set is run on all clinical specimens tested with the EV-D68 2014 rRT-PCR as a measure of the presence and quality of nucleic acid resulting from extraction of the clinical specimens.

The above-described EV-D68 2014 rRT-PCR, when labeled consistently with the labeling authorized by FDA entitled “Enterovirus D68 2014 Real-time RT-PCR Assay Instructions for Use” (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 EV-D68 2014 rRT-PCR 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 CDC’s Enterovirus D68 2014 Real-time RT-PCR Assay (EV-D68 2014 rRT-PCR) Results
- Fact Sheet for Patients: Understanding Results from the Enterovirus D68 2014 Real-time RT-PCR Assay (EV-D68 2014 rRT-PCR)

As described in section IV below, CDC and any authorized distributor(s) are also authorized to make available additional information relating to the emergency use of the authorized EV-D68 2014 rRT-PCR 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 EV-D68 2014 rRT-PCR in the specified population, when used for the *in vitro* qualitative detection of EV-D68 strains detected in North America 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 EV-D68 2014 rRT-

PCR may be effective in the diagnosis of EV-D68 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 EV-D68 2014 rRT-PCR, when used to diagnose EV-D68 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 EV-D68 2014 rRT-PCR 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 described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the EV-D68 2014 rRT-PCR described above is authorized to diagnose EV-D68 infection in individuals with signs and symptoms of EV-D68 infection and/or epidemiologic 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 EV-D68 2014 rRT-PCR 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 EV-D68 2014 rRT-PCR.
- 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:

CDC and Any Authorized Distributor(s)

- A. CDC and any authorized distributor(s) will distribute the authorized EV-D68 2014 rRT-PCR with the authorized labeling, as may be revised only by CDC in consultation with FDA, to qualified laboratories designated by CDC.

- B. CDC and any authorized distributor(s) will provide to qualified laboratories designated by CDC the authorized EV-D68 2014 rRT-PCR Fact Sheet for Health Care Providers and the authorized EV-D68 2014 rRT-PCR Fact Sheet for Patients.
- C. CDC any authorized distributor(s) will make available on their websites the EV-D68 2014 rRT-PCR Fact Sheet for Health Care Providers and the authorized EV-D68 2014 rRT-PCR Fact Sheet for Patients.
- D. CDC and any authorized distributor(s) will inform qualified laboratories designated by CDC and relevant public health authority(ies) of this EUA, including the terms and conditions herein.
- E. CDC and any authorized distributor(s) will ensure that qualified laboratories designated by CDC using the authorized EV-D68 2014 rRT-PCR 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, CDC and any authorized distributor(s) will maintain records of device usage.
- G. CDC 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 CDC and any authorized distributor(s) become aware.
- H. CDC and any authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized EV-D68 2014 rRT-PCR that is consistent with, and does not exceed, the terms of this letter of authorization.

CDC

- I. CDC will notify FDA of any authorized distributor(s) of the EV-D68 2014 rRT-PCR, including the name, address, and phone number of any authorized distributor(s).
- J. CDC 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. CDC only may request changes to the authorized EV-D68 2014 rRT-PCR Fact Sheet for Health Care Providers or the authorized EV-D68 2014 rRT-PCR Fact Sheet for Patients. Such requests will be made only by CDC in consultation with FDA.
- L. CDC may request the addition of other specimen types for use with the authorized EV-D68 2014 rRT-PCR. Such requests will be made by CDC in consultation with, and require concurrence of, FDA.

- M. CDC may request the addition of other extraction methods for use with the authorized EV-D68 2014 rRT-PCR. Such requests will be made by CDC in consultation with, and require concurrence of, FDA.
- N. CDC may request the addition of other real-time PCR instruments for use with the authorized EV-D68 2014 rRT-PCR. Such requests will be made by CDC in consultation with, and require concurrence of, FDA.
- O. CDC will track adverse events and report to FDA under 21 CFR part 803.

Qualified Laboratories Designated by CDC

- P. Qualified laboratories designated by CDC will include with reports of the results of the EV-D68 2014 rRT-PCR 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.
- Q. 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.
- R. Qualified laboratories designated by CDC will collect information on the performance of the assay, and report to CDC and any authorized distributor(s) any suspected occurrence of false positive or false negative results of which they become aware.
- S. All laboratory personnel using the assay will be appropriately trained on the use of the EV-D68 2014 rRT-PCR on the specified Applied Biosystems PCR instrument systems or other authorized instruments, and use appropriate laboratory and personal protective equipment when handling this test.

CDC, Any Authorized Distributors, and Qualified Laboratories Designated by CDC

- T. CDC, any authorized distributor(s), 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

- U. All advertising and promotional descriptive printed matter relating to the use of the authorized EV-D68 2014 rRT-PCR 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.
- V. All advertising and promotional descriptive printed matter relating to the use of the authorized EV-D68 2014 rRT-PCR 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 qualified laboratories designated by CDC;
- This test has been authorized only for the detection of EV-D68; 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 EV-D68 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 EV-D68 2014 rRT-PCR may represent or suggest that this test is safe or effective for the diagnosis of EV-D68.

The emergency use of the authorized EV-D68 2014 rRT-PCR 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 EV-D68 is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Sincerely,

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

Enclosure