

September 18, 2020

George De La Rosa
Manager II, Regulatory Affairs
Bio-Rad Laboratories, Inc.
5731 West Las Positas Blvd.
Pleasanton, CA 94588

Device: Bio-Rad SARS-CoV-2 ddPCR Kit

Company: Bio-Rad Laboratories, Inc.

Indication: Qualitative detection of nucleic acid from SARS-CoV-2 in nasopharyngeal, oropharyngeal, anterior nasal and mid-turbinate nasal swabs, nasopharyngeal washes/aspirates and nasal aspirates, as well as bronchoalveolar lavage (BAL) specimens collected from individuals suspected of COVID-19 by their healthcare provider. Emergency use of this test is limited to authorized laboratories.

Authorized Laboratories: Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet requirements to perform high complexity tests.

Dear Mr. De La Rosa:

On May 1, 2020, based on your¹ request, the Food and Drug Administration (FDA) issued a letter authorizing the emergency use of your product,² for the qualitative detection of nucleic acid from SARS-CoV-2 in nasopharyngeal, anterior nasal and mid-turbinate nasal swab specimens as well as nasopharyngeal wash/aspirate and nasal aspirate specimens collected from individuals suspected of COVID-19 by their healthcare provider, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3). The May 1, 2020, letter authorizing emergency use of this test limited testing to laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform high complexity tests.

On August 31, 2020, you requested to amend your Emergency Use Authorization (EUA). Based on that request, and having concluded that revising the May 1, 2020, 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)), FDA is reissuing the May 1, 2020 letter in its entirety with the revisions incorporated³. Pursuant to section 564 of the Act and the Scope of Authorization (Section II)

¹ For ease of reference, this letter will use the term “you” and related terms to refer to Bio-Rad Laboratories, Inc.

² For ease of reference, this letter will use the term “your product” to refer to the Bio-Rad SARS-CoV-2 ddPCR Kit used for the indication identified above.

³ The revisions to the May 1, 2020 letter include: (1) change of the device name from “Bio-Rad SARS-CoV-2

and Conditions of Authorization (Section IV) of this reissued letter, this test is now intended for the indications described above.

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is 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 the virus that causes COVID-19. Pursuant to Section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of the virus that causes COVID-19 subject to the terms of any authorization issued under Section 564(a) of the Act.⁴

FDA considered the totality of scientific information available in authorizing the emergency use of your product for the indication above. A summary of the performance information FDA relied upon is contained in the Instructions for Use (identified below).

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of your product, described in the Scope of Authorization of this letter (Section II), subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of your product meets the criteria for issuance of an authorization under Section 564(c) of the Act, because I have concluded that:

1. The SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;
2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that your product may be effective in diagnosing COVID-19, and that the known and potential benefits of your product when used for diagnosing COVID-19, outweigh the known and potential risks of your product; and,
3. There is no adequate, approved, and available alternative to the emergency use of your product.⁵

II. Scope of Authorization

ddPCR Test” to “Bio-Rad SARS-CoV-2 ddPCR Kit,” (2) optimize the assay workflow related to sample input and elution volumes for nucleic acid extraction and the ddPCR reaction volume, (3) lower (more sensitive) assay LoD, (4) update the control results interpretation in terms of copies/μL and number of positive droplets, and (5) update the Instructions for Use to reflect assay optimization, new improved LoD, and expected performance of the controls. and (6) update labeling to reflect language more consistent with recent authorizations.

⁴ U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act*, 21 U.S.C. § 360bbb-3. 85 FR 7316 (February 7, 2020).

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

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited to the indication above.

Authorized Product Details

Your product is a a partition-based endpoint RT-PCR test intended for the qualitative detection of nucleic acid from SARS-CoV-2 in nasopharyngeal, oropharyngeal, anterior nasal and mid-turbinate nasal swabs, nasopharyngeal washes/aspirates and nasal aspirates, as well as bronchoalveolar lavage (BAL) specimens collected from individuals suspected of COVID-19 by their healthcare provider. The SARS-CoV-2 nucleic acid is generally detectable in respiratory specimens during the acute phase of infection. Positive results are indicative of the presence of SARS-CoV-2 nucleic acid; clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. Positive results do not rule out bacterial infection or co-infection with other viruses. Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.

To use your product, SARS-CoV-2 nucleic acid is first extracted, isolated and purified from nasopharyngeal, oropharyngeal, anterior nasal, mid-turbinate nasal swabs, nasopharyngeal washes/aspirates and nasal aspirates, or BAL specimens. Using the Bio-Rad One-Step RT-ddPCR Advanced Kit for Probes the purified nucleic acid and mastermix RT-ddPCR mixtures are fractionated into up to 20,000 nanoliter-sized droplets in the form of a water-in-oil emulsion in the Automated Droplet Generator, or other authorized instrument (as may be requested under Condition M below). The emulsions are then thermocycled to achieve reverse transcription to generate cDNA followed by target amplification plus probe hydrolysis in each droplet. Subsequent to PCR, the fluorescence intensity of each droplet is measured in two channels (FAM and HEX) in the Droplet Reader, or other authorized instrument. The fluorescence data is then analyzed by the QuantaSoft v1.7 Software and QuantaSoft Analysis Pro v1.0 Software, or other authorized software to determine the presence of SARS-CoV-2. The Bio-Rad SARS-CoV-2 ddPCR Kit includes the following materials or other authorized materials: 2019-nCoV CDC ddPCR Triplex Probe Assay, One-Step RT-ddPCR Advanced Kit for Probes (Supermix, Reverse Transcriptase, Dithiothreitol (DTT)), Exact Diagnostic SARS-CoV-2 Standard, and Exact Diagnostic SARS-CoV-2 Negative.

Your product requires the following control materials, or other authorized control materials (as may be requested under Condition M below), that are processed in the same way as the patient samples and are required to be included with each batch of specimens tested with your product. All controls listed below must generate expected results in order for a test to be considered valid, as outlined in the Instructions for Use:

- Internal Control - Detection of human RNase P (RP) acts as an internal control for each clinical specimen and controls for specimen integrity, properly performed processing, including extraction, and PCR.
- SARS-CoV-2 Positive Control - Exact Dx SARS-CoV-2 Standard contains *in vitro* transcribed SARS-CoV-2 RNA with genomic regions targeted by the kit. The positive control is used to monitor for failures of rRT-PCR reagents and reaction conditions.
- Extraction Control (EC) – the Exact Dx SARS-CoV-2 Negative Control is used as an

extraction control and consists of total nucleic acids extracted from a noninfectious cultured human cell material. Used as an extraction control and positive control for the RP primer and probe set.

- No Template (Negative) Control - Nuclease-free, molecular-grade water used to monitor non-specific amplification, cross-contamination during experimental setup, and nucleic acid contamination of reagents.

Your product also requires the use of additional authorized materials and authorized ancillary reagents that are not included with your product and are described in the Instructions for Use.

The above described product, when labeled consistently with the labeling authorized by FDA, entitled “Bio-Rad SARS-CoV-2 ddPCR Kit Instructions for Use” (available at <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas>), and the following product-specific information pertaining to the emergency use, which is required to be made available to healthcare providers and patients:

- Fact Sheet for Healthcare Providers: Bio-Rad SARS-CoV-2 ddPCR Kit
- Fact Sheet for Patients: Bio-Rad SARS-CoV-2 ddPCR Kit

The above described product, when accompanied by the Instructions for Use (identified above) and the two Fact Sheets (collectively referenced as “authorized labeling”) is authorized to be distributed to and used by authorized laboratories under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

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 your product, when used consistent with the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of your 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 your product may be effective in diagnosing COVID-19, when used consistent with the Scope of Authorization of this letter (Section II), 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 your product (as described in the Scope of Authorization of this letter (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product 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) of the Act described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1) of the Act, your product is authorized for the indication above.

III. Waiver of Certain Requirements

I am waiving the following requirements for your product 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 your product, but excluding Subpart H (Acceptance Activities, 21 CFR 820.80 and 21 CFR 820.86), Subpart I (Nonconforming Product, 21 CFR 820.90), and Subpart O (Statistical Techniques, 21 CFR 820.250).

IV. Conditions of Authorization

Pursuant to Section 564(e) of the Act, I am establishing the following conditions on this authorization:

Bio-Rad Laboratories, Inc. (You) and Authorized Distributor(s)⁶

- A. Your product must comply with the following labeling requirements pursuant to FDA regulations: 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).
- B. You and authorized distributor(s) will make your product available with the authorized labeling to authorized laboratories.
- C. You and authorized distributor(s) will make available on your website(s) the authorized Fact Sheet for Healthcare Providers and the Fact Sheet for Patients.
- D. You and authorized distributor(s) will inform authorized laboratories and relevant public health authorities of this EUA, including the terms and conditions herein, and any updates made to your product, authorized labeling and authorized Fact Sheets.
- E. Through a process of inventory control, you and authorized distributor(s) will maintain records of the authorized laboratories to which they distribute the test and number of tests they distribute.
- F. You and authorized distributor(s) will collect information on the performance of your product. You will report to FDA any suspected occurrence of false positive and false negative results and significant deviations from the established performance characteristics of the product of which you become aware.

⁶ “Authorized Distributor(s)” are identified by you, Bio-Rad Laboratories, Inc., in your EUA submission as an entity allowed to distribute your device.

- G. You and authorized distributor(s) are authorized to make available additional information relating to the emergency use of your product that is consistent with, and does not exceed, the terms of this letter of authorization.

Bio-Rad Laboratories, Inc. (You)

- H. You will notify FDA of any authorized distributor(s) of your product, including the name, address, and phone number of any authorized distributor(s).
- I. You will provide authorized distributor(s) with a copy of this EUA and communicate to authorized distributor(s) any subsequent amendments that might be made to this EUA and its authorized accompanying materials (e.g., Fact Sheets).
- J. You will comply with the following requirements under FDA regulations: Subpart H (Acceptance Activities, 21 CFR 820.80 and 21 CFR 820.86), Subpart I (Nonconforming Product, 21 CFR 820.90), and Subpart O (Statistical Techniques, 21 CFR 820.250).
- K. You must have lot release procedures and the lot release procedures, including the study design and statistical power, must ensure that the tests released for distribution have the clinical and analytical performance claimed in the authorized labeling.
- L. If requested by FDA, you must submit lot release procedures to FDA, including sampling protocols, testing protocols, and acceptance criteria, that you use to release lots of your product for distribution in the U.S. If such lot release procedures are requested by FDA, you must provide it within 48 hours of the request.
- M. You may request changes to this EUA for your product, including to the Scope of Authorization (Section II in this letter) or to the authorized labeling, including requests to make available additional authorized labeling specific to an authorized distributor. Such additional labeling may use another name for the product but otherwise must be consistent with the authorized labeling, and not exceed the terms of authorization of this letter. Any request for changes to this EUA should be submitted to the DMD/OHT7-OIR/OPEQ/CDRH and require appropriate authorization from FDA prior to implementation.
- N. You will evaluate the analytical limit of detection and assess traceability⁷ of your product with any FDA-recommended reference material(s). After submission to and concurrence with the data by FDA, you will update your labeling to reflect the additional testing. Such labeling updates will be made in consultation with, and require concurrence of, DMD/OHT7-OIR/OPEQ/CDRH.
- O. You will have a process in place for collecting and reporting, and will report to FDA pursuant to 21 CFR Part 803, adverse events (including any occurrence of false results) of which you become aware.

⁷ Traceability refers to tracing analytical sensitivity/reactivity back to an FDA-recommended reference material.

Authorized Laboratories

- P. Authorized laboratories using your product will include with test result reports, all authorized Fact Sheets. Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.
- Q. Authorized laboratories using your product will use your product as outlined in the authorized labeling. Deviations from the authorized procedures, including the authorized instruments, authorized extraction methods, authorized clinical specimen types, authorized control materials, authorized other ancillary reagents and authorized materials required to use your product are not permitted.
- R. Authorized laboratories that receive your product will notify the relevant public health authorities of their intent to run your product prior to initiating testing.
- S. Authorized laboratories using your product will have a process in place for reporting test results to healthcare providers and relevant public health authorities, as appropriate.
- T. Authorized laboratories will collect information on the performance of your product and report to DMD/OHT7-OIR/OPEQ/CDRH (via email: CDRH-EUA-Reporting@fda.hhs.gov) and you (1-800-2BIORAD (1-800-224-6723)) any suspected occurrence of false positive or false negative results and significant deviations from the established performance characteristics of your product of which they become aware.
- U. All laboratory personnel using your product must be appropriately trained in ddPCR techniques and use appropriate laboratory and personal protective equipment when handling this kit, and use your product in accordance with the authorized labeling.

Bio-Rad Laboratories, Inc. (You), Authorized Distributors and Authorized Laboratories

- V. You, authorized distributors, and authorized laboratories using your product will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

Conditions Related to Printed Materials, Advertising and Promotion

- W. All descriptive printed matter, including advertising and promotional materials, relating to the use of your product shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.
- X. No descriptive printed matter, including advertising or promotional materials, relating to the use of your product may represent or suggest that this test is safe or effective for the detection of SARS-CoV-2.
- Y. All descriptive printed matter, including advertising and promotional materials, relating to the use of your product 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 authorized laboratories;
- This test has been authorized only for the detection of nucleic acid from SARS-CoV-2, 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 emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

The emergency use of your product 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 and/or diagnosis of COVID-19 is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures