September 4, 2020

Anna Rolda, MS, CLS
Manager, Quality & Regulatory Affairs
BillionToOne, Inc.
1455 Adams Dr. Suite 1110
Menlo Park, CA 94025

Device:	qSanger-COVID-19 Assay
Company:	BillionToOne, Inc.
Indication:	Qualitative detection of nucleic acid from SARS-CoV-2 in upper respiratory specimens (such as nasal swab, mid-turbinate swab, nasopharyngeal swab, and oropharyngeal swab specimens) 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 Ms. Rolda:

This letter is in response to your[1] request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of your product,[2] pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

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.[3]

[1] For ease of reference, this letter will use the term "you" and related terms to refer to BillionToOne, Inc.
[2] For ease of reference, this letter will use the term "your product" to refer to the qSanger-COVID-19 Assay used for the indication identified above.
[3] 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*

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.[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 indication above.

Authorized Product Details

Your product is a Sanger sequencing-based qualitative test for the detection of nucleic acid from SARS-CoV-2 in upper respiratory specimens (such as nasal swab, mid-turbinate swab, nasopharyngeal swab, and oropharyngeal swab specimens) 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.

To use your product, viral transport media from upper respiratory swab specimens is combined with qSanger-COVID-19 RT-PCR master mix without prior extraction and purification of the sample's RNA and is then subjected to a modified Sanger sequencing reaction. In the qSanger-COVID-19 Assay workflow, a spike-in DNA with a sequence that is frameshifted compared to the natural viral nucleocapsid gene sequence of the SARS-CoV-2 virus is introduced as an internal control into the test samples. After the sample derived SARS-CoV-2 RNA is reverse-transcribed to cDNA, the spike-in Internal Control (IC) and the sample derived SARS-CoV-2 cDNA- if present - are co-amplified in an end-point PCR using primers for the nucleocapsid

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Cosmetic Act, 21 U.S.C. § *360bbb-3*. 85 FR 7316 (February 7, 2020).

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

gene of SARS-CoV-2. Subsequent to the RT-PCR step the reaction is cleaned up through an Exo-SAP digestion step and the resulting product is then subjected to BigDye 3.1 chemistry-based Sanger cycle sequencing. In negative samples only, the spike-in frameshifted sequence is found. In positive samples mixed sequences of the natural SARS-CoV-2 target and the frameshifted spike-in sequence is found with a spike-in sequence derived 4 bp tail at the end of the sequence. The qSanger-COVID-19 Assay includes the following materials or other authorized materials: Primers, SARS-CoV-2 spike in sequence, Enzyme Mixes and other necessary reagents.

Your product requires the use of a positive control from the SeraCare AccuPlex SARS-CoV-2 Reference Material Kit, which is available separately and is run as outlined in the Instructions for Use (identified below).

Your product requires the following control materials, or other authorized control materials (as can be requested under Condition N below), that are processed in the same way as the specimens 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:

- AccuPlex SARS-CoV-2 Positive Reference Material - One AccuPlex SARS-CoV-2 Positive control is run for each batch of patient specimens. The AccuPlex positive control is SARS-CoV-2 RNA encapsulated in alpha virus particles and provided in VTM at a concentration of 5 copies/µl. This positive control is a full process control that monitors for the reverse transcription, PCR amplification, and Sanger sequencing reactions in VTM.
- No-RNA negative control - One nuclease-free water negative control is run for each batch of patient specimens. This control ensures that the spike-in amplification and sequencing occurs as expected in the batch and that there is no genomic sequence contamination. The chromatogram for this control must be a pure spike-in sequence, i.e., no 4 bp tail, which indicates a negative result.
- No-Template - No Spike-in control - One control containing nuclease-free water and no spike-in is to be included for each batch of patient specimens. This control ensures that no spike-in contamination is occurring. This control should not have any observable chromatogram sequence, as there is no amplifiable material.
- Spike-in Internal Control - The internal spike-in control is run with every patient specimen and every control. This control is synthetic single stranded DNA that has a 4bp frameshift relative to the SARS-CoV-2 native target sequence. The spike-in internal control is added to the patient specimen VTM prior to reverse-transcription and PCR amplification and remains throughout all subsequent assay steps.

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 labeling entitled “Instructions for Use qSanger-COVID-19 Assay,” the abbreviated “BillionToOne, Inc. qSanger-COVID-19 Assay” Package Insert (supplied with the final packaged kit), and the following product-specific information pertaining to the emergency use, which is required to be made available as set forth in the Conditions of Authorization (Section

IV), are collectively referred to as the "authorized labeling" (available at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations):

- Fact Sheet for Healthcare Providers: BillionToOne, Inc. - qSanger-COVID-19 Assay
- Fact Sheet for Patients: BillionToOne, Inc. - qSanger-COVID-19 Assay

The above described product, with the authorized labeling provided as set forth in the Conditions of Authorization (Section IV), 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 as described within and used consistently 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 for diagnosing COVID-19, when used consistently 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) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), 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:

BillionToOne Inc. (You) and Authorized Distributor(s)[5]

A. Your product must comply with the following labeling requirements under FDA regulations: the intended use statement (21 CFR 809.10(a)(2), (b)(2)); adequate directions for use ((21 CFR 809.10(b)(5), (7), and (8)); 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 include a physical copy of the authorized abbreviated "BillionToOne, Inc. qSanger-COVID-19 Assay" Package Insert and Fact Sheets with your product to authorized laboratories, and will make the "Instructions for Use qSanger-COVID-19 Assay," electronically available with the opportunity to request a copy in paper form, and after such request, promptly provide the requested information without additional cost. You may request changes to the authorized labeling. Such requests will be made in consultation with, and require concurrence of, DMD/OHT7-OIR/OPEQ/CDRH.

C. You and authorized distributor(s) will make available on your website(s) the authorized labeling.

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 and authorized labeling.

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 or false negative results and significant deviations from the established performance characteristics of the product of which you become aware.

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.

BillionToOne Inc. (You)

[5] "Authorized Distributor(s)" are identified by you, BillionToOne Inc., in your EUA submission as an entity allowed to distribute your device.

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 may request 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. Such requests will be made in consultation with, and require concurrence of Division of Microbiology (DMD)/Office of Health Technology 7 (OHT7)-Office of In Vitro Diagnostics and Radiological Health (OIR)/Office of Product Evaluation and Quality (OPEQ)/Center for Devices and Radiological Health (CDRH).

K. 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).

L. 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.

M. 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.

N. 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. Such requests should be submitted to the DMD/OHT7-OIR/OPEQ/CDRH and require appropriate authorizations from FDA prior to implementation.

O. You will evaluate the analytical limit of detection and assess traceability[6] of your product with any FDA-recommended reference material(s). After submission to and concurrence with the data by FDA, you will update labeling to reflect the additional testing. Such labeling updates will be made in consultation with, and require concurrence of, DMD/OHT7-OIR/OPEQ/CDRH.

P. You will track adverse events, including any occurrence of false results and report to FDA pursuant to 21 CFR Part 803.

Authorized Laboratories

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

Q. Authorized laboratories using your product will include with test result reports, all authorized Fact Sheets. Under exigent circumstances, other appropriate methods for disseminating this labeling may be used, which may include mass media.

R. 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.

S. Authorized laboratories that receive your product will notify the relevant public health authorities of their intent to run your product prior to initiating testing.

T. 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.

U. 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 (Website: https://billiontoone.com, email: covid19support@billiontoone.com or by using https://unityscreen.typeform.com/to/vNR12H) 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.

V. All laboratory personnel using your product must be appropriately trained in RT-PCR and Sanger Sequencing techniques and use appropriate laboratory and personal protective equipment when handling this kit, and use your product in accordance with the authorized labeling.

BillionToOne Inc. (You), Authorized Distributors and Authorized Laboratories

W. 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

X. 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.

Y. 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.

Z. 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 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,

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RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures