State of California—Health and Human Services Agency
California Department of Public Health

TOMÁS J. ARAGÓN, M.D., Dr.P.H
Director and State Public Health Officer

GAVIN NEWSOM
Governor

IMPORTANT NOTICE – ACTION NECESSARY

Confirmation of successful transmission by email constitutes proof of receipt of this letter.

June 8, 2021

Adam Rosendorff, MD
CLIA Laboratory Director
CDPH Branch Laboratory
28454 Livingston Ave
Valencia, CA 91355

Timothy Bow
Emergency Procurement Officer, Owner Representative
California Department of Public Health
850 Marina Bay Parkway, Bldg. P
Richmond, CA 94804

STATE: CPH 889339
CLIA: 05D2197416

PUBLIC HEALTH LABORATORY STATE INSPECTION – Routine Inspection
CONDITION REMAINS – Final Request for Information

Dear Laboratory Director/Owner:

In order for a public health laboratory to perform testing under the California Health and Safety Code (HSC) subsections 101160 (a) – (b), it must comply with all federal CLIA requirements. These requirements are found in section 353 of the Public Health Service Act (42 U.S.C. § 263a) and title 42 Code of Federal Regulations part 493 (42 C.F.R. § 493). Compliance with these regulations is a condition of certification for the State Public Health Laboratory Certification program.

An inspection of your laboratory was conducted on December 8, 2020, and December 9, 2020, and on December 16, 2020, by Elsa Eleco, Examiner III, Elaine Flores, Examiner II, Catherine Tolentino, Examiner II, and Jinong Feng, Examiner I, representatives of the California Department of Public Health (the Department), Laboratory Field Services. This routine inspection concluded on February 17, 2021.

As a result of that inspection, Department examiners determined that your laboratory is **not** in compliance with the requirements specified in the Health and Safety Code section 101160 and/or California Code of Regulations, title 17, sections 1078 and 1083.

Department examiners also determined that your laboratory is **not** in compliance with all of the Conditions required for certification in the State Public Health Laboratory Certification program.

In our letter of May 17, 2021, we notified you that your four previous submissions on March 1, March 8, March 11, March 30, 2021, failed to remove all condition level deficiencies.

On May 24, 2021, we received a fifth submission from your laboratory. This submission failed to remove this remaining Condition level deficiency:

- **D5400 - 42 C.F.R section 493.1250 Condition: Analytic systems**

D5400
The allegation of compliance is not credible based on the laboratory's failure to meet the requirements of this Condition. See our review for D5423.

D5423 Establishment of Performance Specifications

42 C.F.R. section 493.1253(b)(2) states:

> "Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable:
>
> (i) Accuracy.
> (ii) Precision.
> (iii) Analytical sensitivity.

(iv) Analytical specificity to include interfering substances.
(v) Reportable range of test results for the test system.
(vi) Reference intervals (normal values).
(vii) Any other performance characteristic required for test performance."

A. Clinical Performance in Asymptomatic Individuals (D5423 1.a., page 62 of the report)

The Emergency Use Authorization (EUA) and Manufacturer Instructions/ Package Insert (IFU) for Perkin Elmer New Coronavirus Nucleic Acid Detection Kit (01/12/2021) indicated, "Perkin Elmer MUST further evaluate the clinical performance from ASYMPTOMATIC individuals in an FDA-agreed upon postauthorization clinical evaluation study within 30 calendar days of the date of this letter. Labeling updates must be made after submission to FDA."

In its May 24, 2021, submission, the laboratory stated: "As agreed upon with the FDA, PerkinElmer (Waltham, MA), will be conducting the post authorization clinical study for the asymptomatic claim in the EUA/IFU version 7 (Please see Attachment D5400_3_PerkinElmer New Coronavirus Nucleic Acid Detection Kit -v7.0). Please reference attachment (Attachment D5400_2_LFS Letter May 2021)."

Attachment D5400_2_LFS Letter May 2021, signed and dated by the Head of Regulatory and Medical Affairs of Perkin Elmer, stated that, "When the study is complete, the kit's instructions for use will be updated with the consultations and concurrence of FDA."

To correct the deficiency, the laboratory must submit the following evidence:

1. Timeline for the study.
   The letter was issued on January 12, 2021, and per the initial statement, "Perkin Elmer MUST further evaluate the clinical performance from ASYMPTOMATIC individuals in an FDA agreed upon postauthorization clinical evaluation study within 30 calendar days of the date of this letter. Labeling updates must be made after submission to FDA."
2. Status of the clinical evaluation. If the evaluation is still in progress, provide the protocol for the study and its initial evaluation.

B. Interpretation of Test Results (D5423 1.f., page 67 of the report)

In its May 24, 2021, submission, the laboratory stated: "The best clinical interpretation for low viral load (high Ct values) was determined by the original laboratory directors Dr. Shantelle Lucas and Dr. Haleh Farzanmehr and subsequently has been reviewed by Dr.

Rosendorff when he joined on January 27, 2021, the California Department of Public Health leadership (CDPH), the CA governor's Testing Task Force (TTF) and other program stakeholders including a team of lab directors from other CDPH laboratories."

Attachment D5400_1, signed and dated on May 14, 2021, by the Office of the State Public Health Laboratory Director, stated the following timeline:

- From November 2, 2020, to November 11, 2020, if a patient specimen received Ct values for the two identified nucleic acid targets of <42, the test result was reported as "positive."
- From November 11, 2020, if a patient specimen received Ct values for the two identified nucleic acid targets of <37, the test result was reported as "positive**."**
- From December 12, 2020, the VBL started reporting Ct values between 37 - 42 using the INC code. From December 12, 2020, to December 16, 2020, the INC code was reported to patients as 'inconclusive."
- Beginning on December 16, 2020, the INC code was reported to patients as 'presumptive positive.'

Attachment D5400_1 also stated:

> **"**At the time of the validation study and review of the report there was not a comparable assay on the market to make a comparison of the higher sensitivity of the assay. Because of this, the laboratory directors were uncomfortable with calling samples in this range as detected. The changes made in December only changed the way the result was worded to the patient. For formal reporting to the state and local health jurisdictions, these results continued to be termed "inconclusive." As transmission rose, and as the state received feedback from patients and partners, we recognized that the term inconclusive was not instructive and did not provide sufficient direction to patients. In order to alleviate confusion, and in the interest of public health given the spike in cases at the time, we provided clearer direction to the patient to isolate and be retested."

Although the letter explained why the laboratory changed the interpretation of patient specimen results, it did not provide the details of the raw data generated at the CDPH Branch Laboratory to support the changes made to the interpretation.

To correct the deficiency, the laboratory must submit the following evidence:

1. A step-by-step validation protocol to support the claim that Ct values between 37-42 are "presumptive positive" and not true negative or true positive. Please submit information that pertains specifically to the CDPH Branch Laboratory. Submit as requested, and do not cross-reference information from an existing IFU of the

manufacturer's EUA.

2. Documentation from current as well as historical data generated at the CDPH Branch Laboratory (Valencia Branch Laboratory) to validate the laboratory's current interpretation of results for "presumptive positive," when the Ct values are between 37 – 42, including:
    a. Historical data (N=study population) to support that 37-42 cycle thresholds are "presumptive positive," and not true negative or true positive.
    b. Original numbers planned/selected, the number used in the final analysis, and the number omitted from the final analysis.
    c. A description of the selection process for the study population.
    d. A list of potential sources of bias. Did you minimize them to avoid inaccurate estimates in your study design and data analysis?
    e. Histograms of results by condition status (if known).

3. The instrument printouts for the study population used to determine that Ct values between 37-42 are "presumptive positive."

4. The final patient test reports that support the instrument printouts.

5. The actual calculation that supports the validation that Ct values between 37-42 are "presumptive positive."

6. A description of the mechanism for data analysis, including:
    a. How was the data imported or processed in the system in order to determine that Ct values between 37-42 are "presumptive positive?"
    b. Was manual import considered or performed during the preparation of the grid?

7. The summary and conclusion of the historical data, including the study population selected in the determination that Ct values between 37-42 are "presumptive positive."

The state of California has adopted the federal CLIA clinical laboratory regulations. As a consequence, the Department determines laboratory compliance based on procedures and guidelines provided by the CLIA program of the Centers for Medicare and Medicaid Services.

In its May 24, 2021, submission, the laboratory referred to the validation experiments it submitted to the Department prior to the laboratory's receipt of its license on October 24, 2021.

- In the course of reviewing procedures initially provided by the laboratory during the initial stages of review for laboratory licensure, Department examiners noticed that the laboratory intended to use Molecular Transport Media (MTM), as opposed to the Viral Transport Media (VTM) prescribed in the IFU of the manufacturer's EUA.
- Because of the planned change in the transport media, the Department asked the laboratory to establish performance characteristics according to 42 CFR § 493.1253(b)(2).
- The experiments conducted on October 19-24, 2021, included accuracy, precision, analytical sensitivity using Molecular Transport Media (MTM).
- The experiments conducted on October 19-24, 2021, did not include any data to support the changes in the result interpretation the laboratory made after receiving its permit to operate a public health branch laboratory.

The laboratory's previous responses and allegations of compliance (March 1, March 8, March 11, March 30, 2021) indicated the following changes in the interpretation of patient specimen results:

- 28Oct2020 – 11Nov2020 – results were reported as per IFU
- 11Nov2020 – 11Dec2020 – a lower Ct cutoff was set for positive results based on Ct value observed during validation, reflecting a change in interpretation from the IFU
- 11Dec2020 – 25Jan2021 – high Ct values (>37 - <42) were interpreted as inconclusive
- 25Jan2021 – present – high Ct values (>37 - <42) were interpreted as presumptive positive

The timeline above indicates the laboratory has not been following the IFU in interpreting patient specimen results since November 11, 2020. This is only eighteen days after the laboratory received the Department's approval for a license to operate a public health branch laboratory.

We reviewed versions 5, 6, 7, and 8 of the manufacturer's IFU. The "Examination and Interpretation of Patient Specimen Results" sections of all these versions of the IFU do not support the changes the laboratory made to the EUA.

Also, if the laboratory made other changes to the EUA, in addition to the interpretation of patient specimen results, the laboratory needs to establish performance specifications in order to comply with 42 CFR § 493.1253(b)(2).

The laboratory has the following options: (1) follow the current EUA; or (2) establish performance characteristics in accordance with 42 CFR § 493.1253(b)(2).

In its May 24, 2021, submission, the laboratory also indicated that it leveraged EUA data "via a Right to Reference letter" and referred to Attachment D5400-9, which is a letter from PerkinElmer's Regulatory and Medical Affairs, the manufacturer of the New Coronavirus Nucleic Acid Detection Kit utilized by the laboratory. The letter was addressed to the laboratory director of the CDPH Branch Laboratory in Valencia. The letter grants the right-to reference to: "(1) Analytical Studies and (2) Inclusivity_Exclusivity."

The FDA defines a Laboratory Developed Test (LDT) as an in vitro diagnostic test that is manufactured by and used within a single laboratory (i.e. a laboratory with a single CLIA certificate). LDTs are also sometimes called in-house developed tests, or "home brew" tests.

The federal CLIA clinical laboratory regulations allow laboratories to utilize LDTs. When a laboratory develops an LDT in-house without receiving FDA clearance or approval, CLIA prohibits the release of any test result prior to the laboratory establishing performance characteristics relating to analytical validity for the use of that test system in the laboratory's own environment. This analytical validation is limited to the specific conditions, staff, equipment, and patient population of the particular laboratory.

The "right-to-reference" invoked by your laboratory is not defined and recognized in the federal CLIA regulations. The summary of the laboratory data you submitted on May 24, 2021, was not generated at the CDPH Branch Laboratory located in Valencia, California. The data submitted was generated by PerkinElmer, the manufacturer of the test.

You may wish to contact the CLIA Program of the Centers for Medicare and Medicaid Services and the Food and Drug Administration regarding your laboratory developed test and ask for further guidance.

We are giving you a **final** opportunity to provide the remaining information identified in our review.

You have 10 CALENDAR DAYS from the date of this notice to provide this office (at the address shown at the end of this notice), with a credible allegation of compliance and acceptable evidence documenting action you have taken to correct all of the Condition level deficiencies in question.

If you submit the requested evidence of correction showing your laboratory has come into Condition-level compliance, postmarked by **June 18, 2021**, and we are able to verify compliance with all CLIA requirements through an on-site follow-up inspection, sanctions will not be imposed. Electronic submission is acceptable.

Please send all correspondence to the following address:

CDPH-Laboratory Field Services
320 West 4th Street, Suite 890
Los Angeles, CA 90013
Attention: Catherine Tolentino, Examiner II

After we have reviewed your response and have determined your compliance, we will conduct an on-site follow-up inspection to verify your laboratory's corrective actions.

If you have any questions regarding this letter, you may contact Catherine Tolentino at 213-422-5703 or via email at Catherine.Tolentino@cdph.ca.gov.

Sincerely,

Elsa Eleco
Section Chief, On-Site Licensing Inspections

cc: Robert J. Thomas
Branch Chief

Catherine J. Tolentino
Examiner II