Puerto Rico Diagnostic Tests Evaluation Commission (PRoDTEC)

Guidelines and Requirements for the Accelerated Emergency Use Consent for Diagnostic Tests, with Special Focus on the Detection of SARS-CoV-2 Testing in CLIA-Certified High Complexity Laboratories in the Commonwealth of Puerto Rico

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I. INTRODUCTION

On February 4, 2020, the Secretary of Health and Human Services (HHS) declared a public health emergency in the United States (US) and its territories because of the emergence of SARS-CoV-2, the virus that causes COVID-19[1]. The declaration was based on the potential impact of CODIV-19 to the health and security of United States citizens in State and Territories or living abroad due to the SARS-CoV-2 virus originally detected in Wuhan City, Hubei Province, China, in 2019[2]. This declaration also justified the eactment of emergency use authorization (EUA) of *in vitro* diagnostics for the detection and diagnosis of novel coronavirus SARS-CoV-2 subject to the terms of any approval issued under section 564(a) of Federal Food, Drug, and Cosmetic (FD&C) Act. Rapid and trustworthy detection of COVID-19 cases requires the availability of *in vitro* diagnostic tests to diagnose cases and monitor the outbreak. Also, cumulative positive results cases coming from patient testing are the hallmark for SARS-CoV-2 transmission dynamics and epidemiological projections that are required to monitor and control COVID-19 spreading. On March 11, 2020, the World Health Organization (WHO), declared that the COVID-19 outbreak outside China has increased 13-fold and declared a pandemic[3].

Accordingly, the Food and Drug Administration (FDA), on February 29, 2020, issued a guidance that is was updated on May 04, 2020, entitled "*Policy for Diagnostic Tests for Coronavirus Disease-2019 during the Public Health Emergency: Immediately in Effect Guidance for Clinical Laboratories, Commercial Manufacturers, and Food and Drug Administration Staff*."[4] This guidance describes a policy involving laboratories employing tests developed and validated before the FDA issued an EUA to achieve rapid testing capacity in the US. This guidance was implemented before public scrutiny because the FDA determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2))[5]. Currently, based on the issued EUA, 22 applications have been granted to test kit manufacturers and commercial laboratories[6].

Also, on March 31, 2020, the FDA concluded that molecular-based laboratory-developed tests (LDTs) that are authorized for use by the singular developing laboratory are appropriate to protect the public health or safety (as described under the Scope of Authorization (Section II)) under section 564 of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 360bbb-3), based only on the current scientific evidence available. Under this EUA, FDA is authorizing tests coming from laboratories certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a to perform high complexity tests for use in the single laboratory. Initially, only the Yale-New Haven Hospital, Clinical Virology Laboratory, has been granted a EUA based on these grounds[7]. Nowadays, more than 179 laboratories have notified the FDA that they have validated their own COVID-19 diagnostic test as set forth in Section IV.A.

Puerto Rico, a territory of the US, has also been affected by the COVID-19 pandemic. By April 11, 2020, official COVID-19 related deaths were 44, and confirmed positive cases were increasing exponentially. With thousands of tests results in backlog, by that date 897 positive cases had been reported by the Department of Health (DoH). A stay-at-home order implemented since March 16 has

[1] *https://www.federalregister.gov/documents/2020/03/06/2020-04630/policy-for-diagnostics-testing-in-laboratories-certified-to-perform-high-complexity-testing-under*
[2] *https://www.fda.gov/media/135010/download*
[3] *https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020*
[4] *https://www.fda.gov/media/135659/download*
[5] *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-face-masks-and-respirators-during-coronavirus-disease-covid-19-public-health*
[6] *https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd*
[7] *https://www.fda.gov/media/136601/download*

probably reduced the number of infections per day but COVID-19 still presents a great risk to Puerto Rico given a healthcare system weakened by several natural disasters and a prolongued fiscal crisis, and a population where over 27% of the 3.2 million people are 60 years old or older[8], among other risk factors. Epidemiological assessments, projections, and mitigation strategies for Puerto Rico are currently hampered by the low number of tests performed in the jurisdiction.

Currently, the testing capacity of the PR State Public Health Laboratory is about +500 tests per day. Initially, most patient samples were sent to offshore laboratories like Quest Diagnostics and LabCorp in the USA with turn-around-times of more than seven days. Now, 7 private high-complexity CLIA-certified diagnostic laboratories in Puerto Rico with high-throughput equipment for COVID-19 diagnostic testing are performing the majority of samples. Together, these laboratories have the capacity to perform several thousand tests daily. One major roadblock is that most of these labs rely mainly on Roche Diagnostics COBAS 6800 equipment and test kits. Roche Diagnostics claims the HHS is controlling the test kits and since Puerto Rico has one of the lowest rates of positive cases per capita (26/100,000), the materials are sent to other states and territories with higher infection rates. There is a great need to implement other diagnostic testing platforms that could augment the number of tests that can be performed locally to mitigate the risk of having diagnostic pipelines being shut down because of lack of reagents.

On March 12, 2020, the FDA, based on the situation that the State of New York is currently enduring, issued enforcement discretion and stated that "it was not objecting to the Wadsworth Center of the New York State Department of Health (Wadsworth Center) authorizing certain laboratories in the State of New York to begin patient testing under certain circumstances to increase the availability of SARS-Cov-2 testing in response to a request from the Wadsworth Center[9]. Historically, all clinical and forensic laboratories and blood banks located in or accepting specimens from New York State must hold a New York State Department of Health clinical laboratory permit. This program is as robust as the requirements established by the College of American Pathologists (CAP) and the Joint Commission (JC). Due to the emergency, Wadsworth Center informed the FDA that they were willing to have laboratories currently licensed by the New York State Department of Health to notify directly to Wadsworth that they have validated their test for COVID-19 and to submit the validation studies directly to them, not to FDA. Also, Wadsworth was required to notify the laboratory if any concerns were identified, request the laboratory to terminate testing when appropiate and mandate issuing a corrected test report indicating that the test result might not be valid.

Moreover, the President of the United States, released on March 13, 2020, a "Memorandum of Expanding State-Approved Diagnostic Tests" (Memorandum)[10]. This Memorandum allowed the Department of Health and Human Services to promulgate policies that enable other states to similarly authorize testing for COVID-19. Under this policy, because the States have oversight responsibility, "*notification of SARS-CoV-2 test validation is not submitted to the FDA, and the laboratory does not submit a EUA request to FDA*". However, the states or territories must notify the FDA if they decide to choose this pathway for enabling test access. The policy leading to an EUA remains unchanged from the initial publication of this guidance on February 29, 2020, though some process updates and clarifications have been made (as further discussed below). The policy for State oversight remains unchanged from the second publication of this guidance on March 16, 2020.

[8] *American Community Survey 2018, US Census*
[9] *https://www.federalregister.gov/documents/2020/03/06/2020-04630/policy-for-diagnostics-testing-in-laboratories-certified-to-perform-high-complexity-testing-under#footnote-1-p13170*
[10] *https://www.whitehouse.gov/presidential-actions/memorandum-expanding-state-approved-diagnostic-tests/*

Based on the current situation faced by Puerto Rico of having a limited capacity for robust diagnostic testing for COVID-19, and past situation with infectious diseases that have merited the development and expedite implementation of new science-based diagnostic methods, we propose the creation of the **Puerto Rico Diagnostic Tests Evaluation Commission** (PRoDTEC). The main purpose of this commission is to accelerate the development of certain laboratory-developed diagnostic tests, with current focus for COVID-19, via a route not leading to an EUA submission as the test will be developed under the authorities of the Commonwealth of Puerto Rico in which the laboratory resides. As such, the Commonwealth of Puerto Rico will assume responsibility for COVID-19 testing by laboratories in its State. This commission is established as stated in Section B. "State Authorization of Laboratories Certified under CLIA that Meet the CLIA Regulatory Requirements to Perform HighComplexity Testing" of the current guidance.

A State or territory choosing to authorize laboratories within that State or territory to develop and perform a test for COVID-19 would do so under authority of its own State law, and under a process that it establishes. FDA does not intend to object to the use of such tests for specimen testing where the notification of SARS-CoV-2 test validation is not submitted to FDA and the laboratory does not submit an EUA request to FDA, and where instead the State or territory takes responsibility for COVID-19 testing by laboratories in its State during the COVID-19 outbreak. FDA requests that the State or territory notify if they choose to use this flexibility to expedite COVID-19 testing. FDA will not be reviewing the process adopted by the State or territory. Currently, the following states have chosen to benefit from this opportunity:

- State of Connecticut
- State of Maryland
- State of Mississippi
- State of Nevada
- State of New Jersey
- State of New York Department of Health Wadsworth Center
- Washington State Department of Health

The PRoDTEC will first propose and submit a protocol for accelerated evaluation of COVID-19 diagnostic tests that may be considered for use in Puerto Rico for approval by Puerto Rico Department of Health (PRDoH) during the COVID-19 emergency. The PRoDTECwill have the responsibility of the accelerated evaluation of diagnostic methodologies and tests for COVID-19 during the public health emergency. The PRoDTEC will be composed of scientific leaders in the fields of biochemistry, molecular biology, clinical laboratory sciences, virology, pathology, epidemiology, and/or other pertaining fields pertinent for the diagnostic test to be evaluated. Upon completing the evaluation, the PRoDTEC will submit its recommendation to the PRDoH for immediate approval. The expectation is that the PRoDTEC science-based evaluation will be completed within days, rather than weeks. This initiative has the aim to help Puerto Rico overcome the emergency that we are facing with COVID-19 by accelerating the availability of COVID-19 diagnostics, that will ultimately help to save lives. The structure of PRoDTEC could be used in the future for expedite implementation of new science-based diagnostic methods.

II. PUERTO RICO DIAGNOSTIC TESTS EVALUATION COMMISSION (PRoDTEC)

The PRoDTEC is a panel of experts coordinated by the PRDoH of the Commonwealth of Puerto Rico, in expediting the revision and approval of use of *in vitro* diagnostic testing for the detection of SARS-CoV-2 virus, responsible for the COVID-19 illness.

Recently, the Secretary of HHS declared a public health emergency in the US and its territories. As a result of this declaration, the FDA issued a "Coronavirus Disease 2019 (COVID-19) Emergency Use Authorizations for Medical Devices"[11] with particular emphasis on *in vitro* diagnostics. In line with the "*Policy for Diagnostic Tests for Coronavirus Disease-2019 during the Public Health Emergency, Immediately in Effect Guidance for Clinical Laboratories, Commercial Manufacturers, and Food and Drug Administration Staff*" issued on the web on May 11, 2020, and the Memorandum issued by the President of the United States, States were allowed to authorized laboratories within the State to develop and perform tests used to detect COVID-19.

Here, we proposed the guidelines that should be followed by the interested laboratories to developed molecular, antigen and serological-based tests laboratory-developed tests (LDTs) for the detection of SARS-CoV-2 during the public health emergency and the use of research use only (RUO) commercially available kits.

III. PRoDTEC COMMISSION

A. Qualifications and appointment of the members

The members of the PRoDTEC Commission will be constituted by eigth (8) members.

Five members will be ex-officio from the PRDoH SARAFS and Deans of the School of Medicine or appropriate representative with the combination of education and/or experience in clinical laboratory sciences.

The other three (3) members are expert representatives from the academia or the private sector with the combination of education and experience in clinical laboratory sciences or related fields.

These experts will be members of the Commision for a term of no more than five (5) years until a successor is named.

The expert representatives need to comply with the following qualifications:

1. Meet the qualifications as a laboratory director of a laboratory performing high complexity testing under the CLIA '88 regulations, Subpart M, Section 493.1443 or hold an earned doctoral degree from an accredited institution in the US or Puerto Rico with a chemical, physical, biological, clinical laboratory science or pathology as the major subject and the physcians board-certified in clinical pathology.
2. Have a minimum of four (4) years of clinical laboratory training or experience on human specimens, or worked in the FDA for at least four (4) years, or a combination

[11] *https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#coronavirus2019*

of both, including at least two (2) years of experience directing, or supervising high complexity testing in at least three (3) of the following clinical laboratory disciplines;

- Chemistry;
- Diagnostic Immunology;
- Hematology;
- Microbiology or Public Health Microbiology;
- Transplant Immunology;
- Clinical Laborotary;
- Molecular Diagnostics

In addition, expert representatives need to have proficiency in the following regulations:

1. Food and Drug Administration (FDA) regulations that cover in vitro diagnostics (IVD) as stated in 21 CFR parts 210, 211, 809, 814, 820, 860, 861, 862, 864, and 866.

2. Strong knowledge of the IVD categorization under the Clinical Laboratory Improvement Amendments (CLIA '88) of 1988.

B. Governance

A nomination committee will review the curriculum vitaes and qualifications of the candidates consider to be members of the commission. The nomination committee will emit a recommendation report to the PRDoH Secretary for nomination of the considered candidates.

The designation of the expert representatives are for the following terms: one (1) for three (3) years, one (1) for four (4) years, and one (1) for five (5) years for the first group. After completing the appointments, the subsequent terms of the expert representatives will be for three (3) years. Any vacancies in the expert representatives before ending of the established term, will be covered by a new compliant nominee, evaluated by the other two members of the committee.

Designated expert representatives to the Commission are not considered public employees, including the dispositions established in the “Ley 1-2012, según enmendada, conocida como “Ley de Ética Gubernamental de Puerto Rico de 2011”.

In case a Commission member has a personal conflict of interest, either institutional or economical that may affect any of the functions appointed in the PRoDTEC, an external adjunct expert can be appointed to help in the process. This adjunct expert must comply with the qualification of an expert representative. In case, more than one expert representative has a personal conflict with the functions appointed in the PRoDTEC, a required number of adjunct experts must be appointed for the process.

One of the expert representatives to the Commission will be named as Leader of the Commission. Another one will be named as Secretary of the Commission.

When two of the three experts of the Commission are present in the scheduled meetings, with the representative of SARAFS (required), will constitute a quorum. Participation of the expert

representatives in the Commission meetings could be in person or by videoconference. Participation of any Commision member as described counts as to be present in the meeting.

The Commission members are not responsible in their personal character in civil cases seeking compensation for damages derived from the ruling taken in the exercise of their functions, unless these actions constitute a violation of the law.

The Commission members could ask for external assistance in exceptional cases.

C. Functions of the PRoDTEC Commission

The PRoDTEC Commission Members have the responsibility of reviewing and emit a recommendation for approval or not approval of the cases submitted by the clinical laboratories.

Application will be reviewed according to the establish guidelines for each test submitted and current FDA and CLIA status and regulations. Approval of the methods will be by unanimous vote.

IV. NOMINATING AND ENVALUATION COMMITTEE

A. Purpose

The Nominating Committee (the "Committee") of the PRoDTEC is established to:

1. Identify persons who possess the qualities needed to become a member of the PRoDTEC.
2. Recommend PRoDTEC Commission Members when a vacancy is created.
3. Evaluate the performance of the Commission.

B. Membership

The Committee shall consist of three (3) members from the Scientific Committee of the Puerto Rico Science, Techonology and Research Trust (PRSTRT). These members must have the combination of education and experience to evaluate the proposed nominees to the Commission. The Committee members shall be scientists with documented experience in biomedical sciences preferentially clinical laboratory sciences and shall serve for such term as the PRSTRT Board of Trustees determines or until a successor is appointed or until their death, resignation or removal. A Chairman will be elected from the members of the committee.

C. Committee Meetings

The Committee shall meet as often as it may deem necessary and appropriate to carry out its roles and responsibilities, but in no event less than once a year. A meeting may be called out by the Chairman of the Committee. All meetings of and other actions by the Committee shall be held or otherwise taken pursuant to the Organization's bylaws, including bylaws provisions governing notice of meeting, waivers thereof, the number of committee members required to take action at meetings or by written consent, and other related matters.

The Committee Chairman shall be responsible for scheduling all meetings and, together with the other members of the Committee, develop a written agenda for each meeting. The Chairman shall preside at the Committee meetings. The Committee shall keep written minutes of meetings, which shall be maintained in the books and records of the Scientific Committee of the PRSTRT.

The Committee may request that any member of the PRoDTEC Commission attend any meeting to provide such information as the Committee request.

D. Duties and Responsibilities

To fulfill its duties and responsibilities, the Committee shall:

1. Annually review and make any appropriate recommendations to the Secretary of Health for further developments and modifications to the Organization governance principles.
2. Develop and recommend Commission membership criteria, since it is important for the members to understand the emerging technologies and innovative business models.
3. Identify, screen, and review individuals qualified to serve as members of the Commission, consistent with qualifications or criteria approved by the Commission.
4. As vacancies or new positions occurs, recommend to the Secretary of Health the appointment of members, taking into account both the desirability of periodic rotation of Commission members and the benefits of continuity and experience of the Commission.
5. Take actions as it deems necessary to encourage continuous improvement of, and foster governance policies, procedures and practices.

E. Evaluation and Reports

The Nominating Committee shall evaluate the Commission performance on an annual basis, including reviewing the Committee's compliance with its charter, and develop criteria for such evaluation. Every two years, the Nominating Committee shall review and assess the adequacy of its charter and recommend any proposed changes to the Scretary of Health for its approval. The Committee may recommend ammendments to this Charter at any time and submit amendments for the approval of the Secretary of Health.

V. SCOPE

The document describes the guidelines for the accelerated evaluation and approval of diagnostics for COVID-19. Specifically, it applies to non-FDA approved molecular, antigen, serological-based or other clinical laboratory tests that are being considered for use in CLIA-certified clinical laboratories in the Commonwealth of Puerto Rico for the detection of SARS-CoV-2 during the public health emergency. This can include both, laboratory-developed tests (LDTs), as well as the validation of commercially available kits that the FDA has so far approved for research use only (RUO). Diagnostic kits that have been already been evaluated by the FDA via the EUA mechanisms are out of the scope of these guidelines[12] and can be used following FDA reporting requirements.

[12] *https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd*

VI. GUIDELINES

Currently, we are enduring a public health emergency in the Commonwealth of Puerto Rico due to the novel coronavirus SARS-Cov-2. Accordingly, it is imperative to take proactive measures to prepare and act to the public health threat involving COVID-19. New diagnostic tests may provide additional results that can inform clinical management among infected persons, add data for epidemiologic monitoring of COVID19, and offer additional public health opportunities or strategies for its control or prevention. Each proposed diagnostic test must be robustly validated to ensure that results obtained from the test meet the expected performance criteria of sensitivity, specifity, and others. The reliability of diagnostic test is essential as its results will have important implications in clinical care as well as public health practice.

In these guidelines, the PRoDTEC describes the process for accelerated approval for the use of RUO commercially available kits and LDT SARS-CoV-2 diagnostics. The review process described is based on the issued enforcement discretion by FDA, and the Memorandum to circumvent EUA submission as the Government of Puerto Rico will be directly revising and approving, as per PRoDTEC expedite revision and recommendation, COVID-19 tests in the island directly.

Commercial manufacturers looking to distribute their SARS-CoV-2 diagnostic tests in other states of the US should follow the traditional EUA submission to FDA route as these policies only applied to Puerto Rico.

Here, the PRoDTEC, in the representation of the Department of Health of the Government of Puerto Rico, provides recommendations for validation of COVID-19 tests. The PRDTEC, upon request, will also consider proposed alternative validation approaches of proposed diagnostic tests on a case-by-case basis.

These guidelines and any recommendations for approval of use will only be valid during the COVID-19 outbreak declared by the Secretary of Health and Human Services until termination of the HHS EUA declaration.

A. Who Can Submit a Request for Accelerated Approval?

Requests of approval of use of LDTs or RUO kits for detection of SARS-CoV-2 is limited to laboratories certified under the Clinical Laboratory Improvement Amendments (CLIA) that meet the CLIA regulatory requirements of 1988 (CLIA), 42 U.S.C. §263a to perform high complexity testing. Interested laboratories must submit evidence of CLIA-certification and any other pertinent information that will support your application (e.g., CAP, JC certifications) to PRoDTEC.

If the test has been previously prohibited distribution by the FDA, PR State accelerated approval can not be requested. We encourage applicants to verify with FDA is a test has been prohibited prior submission.

B. Molecular Diagnostic Tests Validation

The FDA, defines SARS-CoV-2 molecular diagnostic tests as tests that detect SARS-CoV-2 nucleic acids from human specimens. The following validation studies be conducted for molecular SARS-CoV-2 diagnostic tests. LDTs or RUO kits for detection of SARS-CoV-2 must

be validated prior to use. Evidence of the validation must be submitted for revision to PRoDTEC. The following minimum testing is required to be performed to ensure the clinical and analytical validity of the tests:

1. Limit of Detection

Laboratories must document and submit the limit of detection (LoD) of the assay for the detection of SARS-CoV-2. In order to determine the LoD of the assay, either the inactivated virus or RNA spiking into the artificial or real clinical matrix (*e.g.*, Bronchoalveolar lavage [BAL] fluid, sputum, etc.). Also, laboratories should test a dilution series of three replicates per concentration and confirm the final concentration with 20 replicates. The LoD is defined as the lowest concentration at which 19/20 replicates are positive. In the case in where multiple clinical matrices are going to be tested, results from the most challenging matrix is only required.

2. Inclusivity

An *in silico* analysis should be performed to establish the percent identity matches against publicly available SARS-CoV-2 sequences detected by the tests. All the published SARS-CoV-2 sequences must be detectable with the primers and probes selected. Sequences can be downloaded from NCBI or GISAID databases.

3. Cross-reactivity

Cross-reactivity wet testing on common respiratory flora and other viral pathogens at concentrations of 10^6 CFU/ml or higher for bacteria and 10^5 pfu/ml or higher for viruses, except for SARS-Coronavirus and MERS-Coronavirus, which can be accomplished by in silico analysis. As an alternative*, in silico* analysis of the assay primer and probes against common respiratory flora and viral pathogens must be performed for initial clinical use. *In silico* cross-reactivity is defined as greater than 80% homology between one of the primers/probes and any of the sequence present in the targeted microorganism. Sequences can be downloaded from NCBI or GISAID databases. The recommended microorganisms that should be included in the analysis are the following:

Human coronavirus 229E	*Haemophilus influenzae*
Human coronavirus OC43	*Legionella pneumophila*
Human coronavirus HKU1	*Mycobacterium tuberculosis*
Human coronavirus NL63	*Streptococcus pneumoniae*
SARS-coronavirus	*Streptococcus pyogenes*
MERS-coronavirus	*Bordetella pertussis*
Adenovirus (e.g. C1 Ad. 71)	*Mycoplasma pneumoniae*
Human Metapneumovirus (hMPV)	*Pneumocystis jirovecii (PJP)*
Parainfluenza virus 1-4	*Candida albicans*
Influenza A & B	*Pseudomonas aeruginosa*
Enterovirus (e.g. EV68)	*Staphylococcus epidermis*
Respiratory syncytial virus	*Staphylococcus salivarius*
Rhinovirus	Pooled human nasal wash - *to represent diverse microbial flora in the human respiratory tract*
Chlamydia pneumoniae	

4. Clinical Evaluation

This test can be performed with known positive samples or contrived clinical specimens. A minimum of 30 positive/contrived reactive specimens and 30 non-reactive specimens blinded and randomized must be tested to confirm the performance of the test. Contrived reactive specimens can be created by spiking RNA or inactivated virus into leftover individual clinical specimens representing unique patients; most of these specimens can be leftover respiratory specimens such as NP swabs, sputum, etc. Twenty of the contrived clinical specimens should be spiked at a concentration of 1x-2x LoD, with the remainder of specimens spanning the assay testing range. Acceptance criteria for the performance are 95% agreement at 1x-2x LoD, and 100% agreement at all other concentrations and for negative specimens.

C. Antigen Detection Tests

The FDA defines SARS-CoV-2 antigen tests as those that detect proteins that are part of the SARS-CoV-2 virus directly from clinical specimens. The following validation studies be conducted for a SARS-CoV-2 antigen test:

- Limit of Detection/Analytical Sensitivity
- Cross-reactivity/Analytical Specificity
- Microbial Interference
- Clinical Agreement Study

The clinical agreement study is intended to establish the performance characteristics (e.g., sensitivity/PPA, specificity/NPA) of the test. Clinical agreement should be established on human specimens, preferably leftover specimens from patients with or without SARS-CoV-2 infection.

D. Serological Tests

FDA defines SARS-CoV-2 serological tests as tests that identify antibodies (e.g., IgG, IgM) to SARS-CoV-2 from clinical specimens. The following validation studies be conducted for a SARS-CoV-2 serological assay:

- Cross-reactivity/Analytical Specificity
- Class Specificity
- Clinical Agreement Study

The clinical agreement study is intended to establish the performance characteristics (e.g., sensitivity/PPA, specificity/NPA) of the test. FDA recommends that clinical accuracy should be established on human specimens from patients with microbiologically confirmed COVID-19 infection.

VII. APPLICATION REQUIREMENTS

Information must be submitted within 15 business days following successful completion of assay validation requirements. A laboratory seeking approval from the PRoDETC should submit a binder (electronic version accepted) with the following required information about the test:

A. CLIA Certifications

Laboratories submitting an application to the PRoDETC must submit evidence of their CLIA certification and of any other certifications applicable to the application. Only CLIA certified high-complexity laboratories with experience developing and validating molecular diagnostics for viral pathogens are allowed to apply[13].

B. Assay Standard Operating Procedure/Insert

The laboratory should submit the assay standard operating procedure for LDT or the insert and other supporting documentation for RUO tests with the application.

C. Validation Report

A full validation report with all supporting evidence must accompany the application. The following fields must be completed and documented accordingly:

1. Purpose of Submission

Provide a full description of the purpose of your application, including the test name, laboratory(ies) submitting the application, and claimed specimens types (e.g., nasopharyngeal/ oropharyngeal swabs, sputa, BAL, stool, and serum, etc. Also, submit additional testing and confirmation procedures performed upon consultation with the PRoDETC. Positive results should also be reported in accordance with local, state, and federal regulations.

2. Measurand

Please specify the specific nucleic acid sequences from the genome of SARS-CoV-2 targeted in the assay.

3. Laboratory/Sponsor

Document the official name of the laboratory, contact information, and all locations where testing will be performed.

4. Regulatory Status of the Assay

Establish the regulatory status of the assay (i.e., not cleared, CLIA waived, or subject to an approved investigational device exemption.

5. Intended Use

Document the intended use of the assay in terms of the test technology (e.g., RT-PCR, Sanger Sequencing, NGS, etc.)

[13] *The main reason why only CLIA certified high complexity laboratories are allowed to apply is that compliance in other aspects of clinical laboratory testing like personnel, regulatory and infrastructure requirements are covered under CLIA certification.*

6. Instruments Used with Test

Describe all instruments required in where the assay was validated, and it is known to work. Instruments may include different RT-PCR machines, equipment for RNA extraction, software, among others.

7. Test Principle

Describe the main test principle and product overview of the assay in detail.

a) Description of Test Steps

Describe in sufficient detail the procedure for performing the assay in sequential order as a list, including the extraction methodology. Please also include all the names of the equipment used in the assay. If a well-documented laboratory procedure is available, please append it to the report.

b) Controls and Materials Required

Describe the assay controls to be performed in the laboratory, including the positive and negative control; ideally, the positive control will be used to confirm performance near the test LoD. If a template control is used, please describe in general terms the sequence used, the extraction control, and the internal control, if applicable. Please also describe the frequency that controls will be tested.

c) Assay results and interpretation

Explain in detail the results of the test procedure, e.g., reactive (positive/detected), non-reactive (negative/non-detected), or invalid (no result reported).

d) Performance Results

Describe in detail the results of the validation studies, in terms of the LoD - Analytical Sensitivity, Inclusivity (analytical sensitivity), Cross-reactivity (Analytical Specificity), and Clinical Evaluation results.

8. Fact Sheet for Healthcare Providers and Patients

Submit a proposed Fact Sheet for Patients and Healthcare Providers document for revision.

9. Instructions for Use/ Proposed Labeling/Package Insert

Include a detailed package insert or Laboratory SOP/protocol.

10. Record Keeping and Reporting Information Requirements

The laboratory should track adverse events and report to FDA under 21 CFR Part 803. A website is available to report on adverse events, and this website must be referenced in the Fact Sheet for Health Care Providers. The laboratory will maintain information on the performance of the test, and report to the FDA and the PRDoH any suspected change in performance of which they become aware. The laboratory will maintain records associated with the application and ensure these records are maintained until notified by FDA and the PRDoH. Such records will be made available to the FDA and the PRDoH for inspection upon request.