22 April 2020

Stephen M. Hahn, MD
Commissioner of Food and Drugs
Food and Drug Administration
FDA White Oak Campus
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: SARS-CoV-2 / COVID-19 Diagnostics

Dear Commissioner Hahn:

We are writing in regards to the current state of diagnostic testing for SARS-CoV-2/COVID-19. As long-time HIV/AIDS activists from experienced national organizations, working in the research and development field for many years, let us start by saying that we have passed this way before and have learned the hard way from our mistakes. Randomized clinical trials and evidence-based research are urgently critical in the COVID-19 arena. The U.S. Food and Drug Administration (FDA) has a responsibly to exercise its oversight of diagnostics, drug and vaccine development and marketing vigorously, robustly, and proactively.

When the HIV/AIDS movement began almost 40 years ago, the FDA was among our first targets. Over the years, we have worked closely with dedicated, talented, and hard-working FDA professionals, especially at the Center for Drugs Evaluation and Research (CDER). While working with CDER and more recently with (Center for Biologics Evaluation and Research (CBER), we have found your staffers to be brilliant, collegial, honest and totally committed to their work. Their progressive trial designs and policies help ensure that the FDA remains true to its statutory responsibilities while also promoting patient friendly trial designs that are equitable, efficient, and ethical.

We write today because we are extremely dismayed at the state of SARS-CoV-2/COVID-19 diagnostics. Of course, what are needed is a coherent, coordinated and collaborative national COVID-19 testing policies and strategies that include invoking the Defense Production Act (DPA) in order to quickly and continually scale-up testing and avoid the same supply chain bedlam that has occurred with the original Centers for Disease Control and Prevention (CDC) polymerase chain reaction (PCR) diagnostic test for SARS-CoV-2 infection, and more recently with respect to personal protective equipment (PPE), test swabs, testing reagents, critical care interventions, and other healthcare supplies. Every component of test kits have been unavailable at one time or another. Testing strategies for SARS-CoV-2 and serology will be wholly unsuccessful without adequate national supply chain policies and strategies.

While we understand that at the outset of the US outbreak, the FDA was between a rock and a hard place, first dealing with a flawed CDC test, part of which was contaminated as a result of substandard quality controls. The agency was then pressured by the Administration to do whatever necessary to increase COVID-19 testing availability for the people of the US in this time of national and global crisis. Nevertheless, the FDA cannot lose sight of the fact that accurate, reproducible diagnostic testing is crucial to assessing accurate viral spread and developing containment strategies. The American public will rely on the FDA to carefully scrutinize all testing devices, not to just quickly get as many tests as possible out the door.

The FDA issued a February 29, 2020 Guidance to begin to address expedited SARS-CoV-2/COVID-19 testing. An expanded guidance which relaxed Emergency Use Approval (EUA) regulations was issued on March 16, 2020.

The expanded guidance which contains very confusing new pathways, Policy A through D, permits manufacturers to begin using testing on patient samples and distributing tests into the marketplace after only limited internal validation, using contrived samples instead of actual patient samples and without any agency vetting. While this may expedite access, it has also created an unregulated rush to market that has caused chaos, resulting in dangerously inaccurate test results.

We now find ourselves in a state of pandemic pandemonium combined with regulatory limbo. It is essential to build an expeditious and evidence-based foundation of accurate SARS-CoV-2/COVID-19 testing to ensure we are on solid ground as we attempt to relax containment strategies, like social distancing, and begin to craft wide-spread future SARS-CoV-2/COVID-19 testing strategies which will enable our economy to safely re-open. Without highly accurate testing results, we are creating a house of cards doomed to failure which will result in continued morbidity and mortality for the American people as well as a continuing economic disaster. We are delighted that you have enlisted the National Institutes of Health (NIH) and the CDC to work with the FDA in this regard.

We will begin by reviewing various COVID-19 tests, noting issues and pitfalls and end with providing short and long-term recommendations.

PCR Testing

We are very concerned about the multiple reports highlighting inaccurate results with the complicated PCR assays currently used to diagnose SARS-CoV-2. It is unclear if these discordant results are due to inherent test designs, sample collection, processing errors or something else.

Like the continual supply chain issues presented with many other essential healthcare items to combat SARS-CoV-2/COVID-19, test kit components necessary to conduct PCR diagnostics are no exception. At various times there have been critical shortages from test kits, reagents, viral transport medium (VTM), and swabs to vials. It is impossible to regularly conduct the most basic testing under these circumstances. It is absurd to believe the testing necessary to relax current social containment restrictions and reopen the economy is possible without an uninterrupted stream of the materials necessary to conduct SARS-CoV-2/COVID-19 testing.

There have been reports of confusion and a lack of real time information regarding which diagnostic tests might be backlogged and which tests are readily available even when public health programs and health providers are trying to diagnose all the seriously ill, protect health workers and first responders, and expand testing to the mild-to-moderately ill or those with documented or possible exposure to SARS-CoV-2. This absence of this information is causing obvious testing delays.

While the FDA has granted EUAs to a number of SARS-CoV-2 PCR test manufacturers, there are many university based labs that are a capable of conducting PCR testing. Increasing accurate testing capacity at university centers would assist their local health departments in testing efforts which would provide more jurisdictions with the ability to relax social containment restrictions and more quickly reopen the economy.

Although the agency has to date only given authorization to LabCorp to market a home testing kit via a re-issued EUA, there are a number of manufacturers advertising unauthorized home swab tests online from a cost of $70 to $181.00. https://www.wellandgood.com/good-advice/covid-19-at-home-test/

This is a violation of the FDA regulations as SARS-CoV-2 testing they have not received FDA approval for home use. We believe this may result in dangerously inaccurate test results with obvious consequences. Home testing

may also result in people wasting much needed testing resources and dollars purchasing home test kits which may provide inaccurate results.

Further, we believe there is no current patient friendly, optimal FDA mechanism to report unauthorized use of COVID-19 testing kits or other fraudulent issues. The MedWatch and Reporting Unlawful Sales of Medical Products on the Internet sections of the FDA website page are complicated, time consuming and difficult to find especially for people who may be recovering from COVID-19. Moreover, they do not directly address the instant problem.

Saliva Testing

The FDA very recently granted EUA to the first SARS-CoV-2 saliva diagnostic test to RUCCDR Infinite Biologics. Studies on this platform are being conducted with a molecular assay from Rutgers University in conjunction with RWJ Barnabas which is collecting the samples. Because these test do not involve nasopharyngeal or oropharyngeal collections, the success of such saliva tests could be instrumental in reducing transmission risk to health care workers and reduced PPE use, including swabs which have been particularly difficult to keep stocked.

These tests have their own sensitivity and specificity issues. Logistics issues are also present. This test needs to be analyzed within 48 hours of collection which can only be performed at a limited number of labs. There have been inaccurate results which may be caused by insufficient amount of saliva or the relocation of the virus into the respiratory tract.

Although the manufacturer claims saliva tests perform as well as other SARS-CoV-2 diagnostics, validation sample sizes remain very small with only 30 samples in the saliva arm and 30 samples in the control arm. Thus, performance accuracy must continue to be monitored.

On the other hand, apparently, 10,000 of these saliva tests can be produced per day which has the potential to advance much needed SARS-CoV-2 testing capacity. The availability of a saliva test may also expand COVID-19 testing to vulnerable populations without access to testing locations.

Vault Health, which is working with Rutgers University in this regard, has developed a SARS-CoV-2 saliva test for home use. Like swab home test manufacturers, Vault Health has apparently interpreted FDA regulations to permit home saliva testing use in conjunction with virtual supervision, and is advertising a home saliva test at a cost of $150.00. We believe this is a violation of its EUA. Again, this may also result in dangerously inaccurate test results, in people wasting much needed testing resources and much needed patient dollars purchasing home test kits which could provide inaccurate results.

Serology Tests

Accurate antibody blood tests that detect evidence of past or ongoing infection with SARS-CoV-2 are essential to identifying who may be safe to re-enter the workface and critical to lifting current workforce restrictions. Inaccurate results are more concerning in this arena as antibody tests will hopefully identify people who may have developed short or longer-term immunity to SARS-CoV-2 reactivation or re-infection. Critical scientific antibody test issues and strategy questions still abound. What is the lowest antibody level that indicates protection? How long is one protected from SARS-CoV-2 reinfection? Could cross-reactivity to other common cold causing coronaviruses provide misleading results? The optimal strategic use of IgG antibodies produced in later stage infection also needs to be established.

Regarding the sensitivity and specificity of the serology assays, given that we do not know the true number of SARS-CoV-2 infections, we also do not know the true incidence or prevalence of SARS-CoV-2. There is a possibility that inaccurate SARS-CoV-2 antibody tests could result in a large percentage of people having false positive results that will probably result in being cleared to return to work, possibly creating new transmission surges.

While we applaud the FDA for enlisting the aid of the NIH and the CDC in assay validation, many issues still remain unresolved. A growing number of inaccurate antibody tests are flooding the market – most of them without even the fig-leaf of an FDA EUA. There are some 90 companies speeding to develop antibody tests with varying degrees of accuracy. Moreover, recent FDA policies that have relaxed regulations have caused confusion as well as permitting false claims of accuracy and FDA approval status. The World Health Organization (WHO) has even recommended against the use of many such tests outside the research setting. Rapid point of care tests administered by provider offices have been aggressively marketed even though federal regulations require that unapproved tests only be administered in high complexity labs.

Policy D of the March 16, 2020 expanded guidance allows manufacturers to distribute tests before receiving EUA if internal manufacturing validation has occurred without FDA or external vetting of any kind. Policy D, as well as a number of the other March 16, 2020 expanded guidance policies, presuppose the manufacturer will apply for an EUA within approximately 15 days. This has opened the floodgates to aggressive marketing of tests with limited accuracy and the loss of a great deal of money on the part of countries like the United Kingdom (UK) that have purchased large quantities of often useless tests.

The FDA recently announced formation of an interagency voluntary validation program that is open to more than 70 Part D serology tests. Although this is a helpful start to addressing validation issues, non-EUA and full approval pathways must be developed with the utmost emphasis on test accuracy in order to prevent even more confusion and chaos. We wonder if streamlining current EUA requirements may possibly be sufficient to accomplish the goals of both evidence-based results as well as expediency.

It is our understanding that the FDA is also still exploring the best way in which test results will be reported, the dissemination method for the protocols to assess test results and the best way to communicate the inherent danger of inaccurate serology test results. Stakeholder engagement may provide helpful information in this regard.

The ultimate decision here is the determination of whether serologic test results from patient samples “can be relied upon and can have a level of accuracy that indicates that these are fit for use in the U.S.”. Timothy Stenzel, Director, FDA Office of In Vitro Diagnostics and Radiological Health (FDA/CDRH Webinar, 25 March 2020). We hope the FDA will be a voice of reason and sanity in these deliberations, making the necessary accuracy decisions and safety pronouncements that will affect the health and wellbeing of the nation for many years to come, especially the poor, the incarcerated, the homeless, immigrants, those with comorbid conditions, and people of color who are experiencing significantly COVID-19-related epidemiologic, healthcare and survival disparities.

Recommendations

1. Continually recommend to the White House Coronavirus Task Force that the nation create a coherent, coordinated and collaborative national COVID-19 testing strategy that includes invoking the Defense Production Act (DPA) in order to successfully scale-up testing kit components to avoid the same

bedlam that has occurred with respect to PPE and critical care interventions and other healthcare supplies;

2. Establish and validate “gold standard” diagnostic tests to which other tests can be compared;
3. Withdraw EUA for any PCR test which cannot provide at least 95% sensitivity and 100% specificity for negative results based on patient samples;
4. Conduct head-to-head of antibody studies, aiming for approval of diversified testing platforms that identify IgG, IgM, and IgG/IgM together;
5. Review and implement when appropriate WHO recommendations against use of inaccurate antibody tests;
6. Require manufacturers to demonstrate test performances with actual patient samples, not contrived samples;
7. Create a public-facing dashboard of accuracy results for each test on the market using clinical data from across the country. Such a system will enable users to have a much better chance of obtaining the most accurate results possible, and will promote more accurate SARS-CoV-2/COVID-19 tracking;
8. Work to create a registry of SARS-CoV-2/COVID-19 related real time test availability information, including location, logistics, shipping and all necessary scientific utilization requirements;
9. Expeditiously create and disseminate protocols that describe how tests will be assessed, and continue to engage with stakeholders in webinars, etc. in an effort to enlist stakeholders in dissemination efforts;
10. Establish mandatory internal validation protocols and continue to work with the NIH and CDC to create external validation programs in an effort to definitively confirm the accuracy of a test for its intended use setting(s);
11. Continue to proactively assist and collaborate in the creation of external validation programs for tests created by universities, academic medical centers, health department, or local laboratories as well as by commercial manufacturers in order increase accuracy, local testing capacity and supplement testing options for local health departments, hospitals and other healthcare providers, promoting jurisdictional ability to develop tests and/or conduct studies and promote the FDA March 16, 2020 Policy B initiative;
12. As more certified PCR labs are established and critical items necessary to PCR testing become available, the FDA should require PCR-certified labs to be operated by skilled laboratories and qualified technicians to avoid contamination and swab mishandling;
13. The number of different PCR tests, saliva and serologic tests is increasing almost daily. As testing capacity is scaled up, the FDA should clarify and tighten Policy A through D pathways created on the March 16, 2020 expanded guidance to ensure that protective safety regulations are being followed and accuracy of SARS-CoV-2/COVID-19 testing results;
14. Establish a process by which tests approved via the FDA EUA mechanism may be withdrawn if the performance of a test is found to be suboptimal;
15. Participate in ultimate decisions relating to how to strategically utilize serologic testing to reopen the economy. All relevant FDA branches, including, but not limited to CDER and CDRH must be involved in strategic discussions to study outstanding scientific issues that will involve clinical trials and scale-up issues, and continue to work with government agencies like CMS to ensure structured changes, such as healthcare reimbursement policies continue to be instituted as the science develops;
16. Quickly issue Warning Letters to companies making dangerous false claims about their test products and FDA approval status, using tests in an unauthorized manner and peddling unauthorized SARS-CoV-2/COVID-19 home test kits;
17. Develop a reporting system on the FDA website separate from MedWatch and Reporting Unlawful Sales of Medical Products on the Internet to report SARS-CoV-2/COVID-19 false claims, unauthorized use and/or fraudulent use of products which is patient friendly and easy to find and navigate.

In conclusion, the current Administration operates within a force field of chaos. SARS-CoV-2/COVID-19 regulatory testing policies and procedures are being directly affected by this dysfunctional dance. The FDA is the nation's gatekeeper, mandated by law and regulation to create order on the basis of evidence-based research. It is imperative that the FDA require evidence-based results, relating to outstanding scientific questions and testing validation and accuracy before granting any sort of approval of SARS-CoV-2COVID-19 devices that will be utilized to relax containment measures and to reopen the U.S. economy. Working with the NIH and the CDC to validate manufacturers' internal test results will undoubtedly aid the agency in this regard. Nevertheless, we hope you will remember that speed is no substitute for accuracy. Premature approval of inaccurate tests will ensure that our efforts to subdue SARS-CoV-2/COVID-19 will be based on a faulty foundation that will be unable to buttress our containment and economic strategies, resulting literally in untold morbidity and mortality to our unprotected citizens who have already suffered enough at the hands of this horrific disease.

We would greatly appreciate a written reply as soon as possible. Your anticipated cooperation is greatly appreciated. Please reply to Lynda Dee: lyndamdee@gmail.com.

Thank you for your many efforts on behalf of the American people.

Respectfully,

Lynda Dee, AIDS Action Baltimore, AIDS Treatment Activists Coalition

Mark Harrington, Treatment Action Group

Ben Cheng, Formerly of Project Inform

Mike Shriver, Formerly of the AIDS Policy Center, UCSF

Jeff Taylor, HIV+ Aging Research Project-Palm Springs

Tim Horn, National Alliance of States and Territorial AIDS Directors

Murray Penner, Prevention Access Campaign

Jules Levin, National AIDS Treatment Advocacy Project

Mitchell Warren, AVAC

cc: Speaker Nancy P. Pelosi
Senator Christopher J. Van Hollen
Anthony S. Fauci, MD
Deborah L. Birx, MD
Brett P. Giroir, MD
Representative. Rosa DeLauro
Representative Lloyd Doggett
Sara Brenner, MD MPH
Elizabeth Hillebrenner,
Timothy Stenzel, MD, PhD

Debra Birnkrant, MD
Jeff Murray, MD, MPH