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Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests (Revised)

Guidance for Test Developers and Food and Drug Administration Staff

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This document supersedes "Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests: Guidance for Test Developers and Food and Drug Administration Staff" issued February 22, 2021.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Office of Product Evaluation and Quality (OPEQ)

Preface

Public Comment

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-0987 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA website titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders, the FDA website titled "Search for FDA Guidance Documents," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents, and the FDA website titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive an additional copy of the guidance. Please include the document number GUI00021004 and complete title of the guidance in the request.

Questions

For questions about this document, contact COVID19Dx@fda.hhs.gov.

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Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests (Revised)

Guidance for Test Developers and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide a policy and recommendations on evaluating the potential impact of emerging and future viral mutations of SARS-CoV-2 on COVID-19 tests. This guidance describes a policy for test developers to consider the impact of emerging and future variants on their COVID-19 tests during development and post-authorization. Throughout this guidance, references to COVID-19 tests are referring to molecular and antigen tests that detect the SARS-CoV-2 virus and serology tests that detect antibodies to the SARS-CoV-2 virus.

This policy is intended to remain in effect only for the duration of the declaration under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) by the Secretary of Health and Human Services (HHS) on February 4, 2020, declaring that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of the novel coronavirus (2019-nCoV).[1] FDA continues to assess the evolving situation and intends to update this guidance as appropriate.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as

[1] *See* 85 FR 7316; *available at* https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.

recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, the Secretary of HHS issued a declaration of a public health emergency under section 319 of the Public Health Services Act related to COVID-19 and mobilized the Operating Divisions of HHS.[2] On February 4, 2020, the Secretary of HHS issued a declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of SARS-CoV-2 based on the HHS Secretary's public health emergency determination under section 564(b)(1)(C) of the FD&C Act.[3] In addition, on March 13, 2020, there was a Presidential declaration of a national emergency in response to COVID-19.[4]

The SARS-CoV-2 virus has mutated over time, resulting in genetic variation in the population of circulating virus variants over the course of the COVID-19 pandemic, with new variants of the virus documented in the United States and globally. Sometimes new variants emerge and disappear, and other times new variants persist and increase in prevalence.

SARS-CoV-2 was first identified in Wuhan, China, and in January 2020, the first genetic sequence (Wuhan-Hu1) was made publicly available. Many tests were developed using this sequence. Antigens and antibodies were also derived from the virus with this sequence. Isolate USA-WA1/2020 was then isolated in the United States from a sample taken from a patient with a respiratory illness who had recently returned to Washington State from travel to the affected region of China and developed clinical disease (COVID-19) in January 2020. Over time, SARS-CoV-2 accumulated mutations and has diversified into a myriad of lineages, including variants with increased transmission rates, such as the B.1.1.7 variant (UK VOC-202012/01), B.1.351 variant (South Africa: 20H/501Y.V2) and P.1 variant (Brazil: 20J//501Y.V3). The omicron variant, B.1.1.529, of SARS-CoV-2, was designated by the United States as a Variant of Concern (VOC)[5] on November 30, 2021. Since the first confirmed case of omicron in the United States was identified on December 1, 2021, this variant and its sub-variants (for example, lineages BA.1, BA.2, BA.2.12.1, BA. 4, BA.5, BE.1, BQ.1/BQ.1.1, etc.) have come to dominate the circulation of SARS-CoV-2 in the United States. The omicron variant has significantly more mutations than previous SARS-CoV-2 variants, particularly in its S-gene, the gene that encodes the virus's spike

[2] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued on Jan. 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.
[3] 85 FR 7316; *available at* https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[4] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), *available at* https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.
[5] For more information, see CDC SARS-CoV-2 Variant Classifications and Definitions at https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html

protein. Sub-variants of omicron may additionally differ in specific mutations or properties.

The terms mutation (or viral mutation, genetic mutation, etc.) and variant (or virus variant, genetic variant, etc.) are used when describing changes in the genetic sequences of SARS-CoV-2. A mutation is an individual genetic change in a SARS-CoV-2 virus sequence when compared with a reference sequence such as Wuhan-Hu1 or USA-WA1/2020. A new virus variant of SARS-CoV-2 has one or more mutations that differentiate it from the reference sequence or predominant virus variants already circulating in the general population. Variants of SARS-CoV-2 are identified by genomic sequences that contain mutation(s) in the RNA genome, which could result in amino acid substitutions, insertions, and/or deletions in viral proteins. Different variants can result in different phenotypes (e.g., a difference in antigenicity, transmissibility, or virulence).

The presence of SARS-CoV-2 mutations in the SARS-CoV-2 virus in a patient sample can potentially change the performance of a test. The clinical impact of mutations on a test's performance is influenced by various factors.

Molecular tests are designed to detect the virus by targeting a specific region(s) of the viral genome. False negative results may occur if mutations are in the part of the viral genome assessed by that test and reduce a test's ability to detect the virus's RNA genome. Molecular tests designed to detect multiple SARS-CoV-2 genetic targets are less susceptible to the effects of genetic variation than tests designed to detect a single genetic target. The impact of genetic variants on molecular test performance is influenced by the sequence of the variant, the design of the test, and the prevalence of the variant in the population. If the test fails to detect a virus variant and the variant increases in prevalence in a community, there may be an increase in the percentage of false negative results.

Changes in the viral genome can result in changes to viral proteins and, therefore, can also impact the performance of an antigen or serology test.

Antigen tests are designed to detect specific viral proteins. If changes in the viral genome alter the structure of a viral protein targeted by an antigen test, the test may not detect the virus, even if the virus is present, leading to false negative results. The impact of genetic variants on test performance is influenced by the type of change to the protein(s), the design of the test, and the prevalence of the variant in the population.

Serology tests may be designed to detect antibodies produced when the body has an adaptive immune response to an infection. Genetic variants may result in changes to the proteins that elicit an antibody response to the virus and the resulting antibody response. If a serology test is designed to detect antibodies using a particular protein(s), the test may not detect antibodies generated in response to an altered protein configuration. This may result in a false negative test result when antibodies to the virus are present but are not detected by the test. The impact of genetic variants on test performance is influenced by the protein impacted by the genetic change, the type of change to the protein, the resulting change to the antibody response, the design of the test, and the prevalence of the variant in the population.

FDA has collaborated with stakeholders to better understand the public health impact of new virus variants and their impact on test performance, has been routinely monitoring publicly available

databases and has coordinated efforts to evaluate the impact of new virus variants on tests that have received Emergency Use Authorization (EUA), as well as tests that were authorized or cleared under the de novo or 510(k) pathway, respectively. Since molecular tests target specific regions of the viral genome, the FDA is monitoring the potential effects of genetic variation on FDA-authorized molecular tests and has been doing so on an ongoing basis throughout the pandemic. As viral mutations can also impact performance of antigen and serology tests, the FDA is also considering the best approach to monitoring the potential effects on EUA-authorized antigen diagnostic and EUA-authorized serology tests as well as on such tests that receive marketing authorization or clearance.

One aspect of FDA's monitoring program involves analyzing available sequence data from publicly available genomic databases, such as the GISAID[6] database. Most SARS-CoV-2 mutations in regions of the viral genome which are targeted by authorized molecular tests appear to be present in sequence databases at very low frequency. FDA believes that when these types of mutations are observed in a sequence database at a significant frequency, such as greater than 5% (when considering at least 2000 sequences over a recent period of time, such as the past week, month, or quarter), this may signify that the mutation is present in an increasing proportion of infected individuals in the United States. In addition to mutations appearing in greater than 5% of sequences in the database, any variant with multiple credible reports (e.g., peer-reviewed literature or, in the more immediate term, reports from the public health community, such as state public health laboratories) indicating the potential to impact patient care practices, increased virulence, or increased transmission risk are more closely monitored by FDA because of the possible increased public health risk.

The FDA regularly monitors EUA-authorized molecular tests, as well as molecular tests that were authorized or cleared under the de novo or 510(k) pathway, respectively, by aligning the tests' primer/probe sequences (or equivalent if the test uses an alternative amplification approach) with the U.S. SARS-CoV-2 genomes published in the GISAID and other databases to determine whether there are any mutations in the region(s) of the viral genome targeted by the tests, as that may impact test performance. After identifying any mutations that may impact test performance, FDA also considers other information such as where the mutation(s) occur in the relation to the test's primer(s) or probe(s), as well as whether there may be multiple mutations that impact a single test, and whether there is the potential for an aggregate of mutations that could impact a particular test and reduce performance.

This program, including follow-up investigations by certain test developers at FDA's request, resulted in FDA releasing a January 8, 2021, safety alert to clinical laboratory staff and healthcare providers about the potential impact of emerging variants, including the B.1.1.7 variant from the United Kingdom, on test performance.[7] Based on additional information from this monitoring, FDA developed a web page, SARS-CoV-2 Viral Mutations: Impact on COVID-19 Tests,[8] to provide updates about the impact of viral mutations on COVID-19 tests. FDA continues to monitor

[6] GISAID is a global science initiative and primary source that provides open-access to genomic data of influenza viruses and the novel coronavirus responsible for COVID-19 (https://www.gisaid.org/).
[7] https://www.fda.gov/medical-devices/letters-health-care-providers/genetic-variants-sars-cov-2-may-lead-false-negative-results-molecular-tests-detection-sars-cov-2
[8] https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests

signals concerning variants and COVID-19 authorized tests and will provide additional information to stakeholders and the public as more information becomes available. This guidance is part of those efforts and includes FDA's recommendations based on the information available at this time. In the current version of this guidance, FDA has provided updated information on actions FDA has taken since the original issuance and has revised the duration for which the policies in this guidance are intended to remain in effect; the recommendations and policies have not been revised.

III. Scope

The recommendations that follow are intended to be used by developers of SARS-CoV-2 molecular, antigen, and serology tests that have been issued an EUA, developers whose tests fall within the policies outlined in the FDA guidance Policy for Coronavirus Disease-2019 Tests (Revised),[9] and other developers pursuing an EUA from FDA for COVID-19 molecular, antigen, and serology tests.

IV. Recommendations

This guidance describes FDA's recommendations for evaluating the potential impact of emerging and future viral mutations of SARS-CoV-2 on COVID-19 tests. There are recommendations for developers with tests not yet authorized (e.g., regarding test development and EUA requests) as well as recommendations for test developers with authorized tests. FDA will continue to reevaluate and update these recommendations as appropriate based on available information.

Additionally, FDA has included conditions of authorization in test EUAs related to evaluating the impact of virus mutation on test performance, including relating to some of the recommendations discussed in this guidance. Test developers of EUA-authorized tests are required to comply with such conditions. With respect to premarket submissions, FDA has established special controls, including one regarding the continuous monitoring, identification, and handling of genetic mutations, when issuing the regulation 21 CFR 866.3981 for devices to detect and identify nucleic acid targets in respiratory specimens from microbial agents that cause the SARS-CoV-2 respiratory infection and other microbial agents when in a multi-target test.[10]

During FDA's review of an EUA request or a marketing submission for a COVID-19 test, FDA intends to consider the performance of the test across all known variants, as well as the developer's plans for post-authorization monitoring. FDA recommends that test developers address in their EUA request or marketing submission whether the labeling should include statements or limitations indicating the time period during and geographic location of which clinical specimens used in the test's evaluation were collected, noting that the clinical performance has not been established in all circulating variants, and that performance may vary depending on the variants, and their prevalence, circulating at the time of patient testing.

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-revised

[10] *See* DEN200031 BioFire Respiratory Panel 2.1 (RP2.1), *available at*: https://www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200031.pdf

FDA will work with test developers of previously authorized tests to determine whether such statements, or other updates, are needed for those tests' authorized labeling.

For tests that are being offered for clinical use as described in the Policy for Coronavirus Disease-2019 Tests (Revised),[11] FDA recommends test developers consider the previously described factors and include such statements in the test labeling as applicable for their test.

FDA also intends to communicate relevant information about the impact of viral mutation on COVID-19 tests to stakeholders, as appropriate, such as in safety alerts and on FDA's website.[12]

A. Recommendations for Developers of Molecular Diagnostic Tests

Since the performance of a diagnostic test can be impacted by viral mutation, FDA recommends that developers: 1) design their test to minimize the impact of viral mutations on test performance; 2) routinely monitor for viral mutations that may impact test performance; and 3) clearly convey any test limitations in the test's labeling as discussed above. These recommendations are explained more throughout this section.

While tests for viral genotyping of new variants may be helpful for monitoring the spread of viral mutations in SARS-CoV-2, it remains unknown whether there is a clinical need for such tests to manage patient care. Tests designed to target and detect specific known variants are likely to become obsolete quickly, as the virus continues to mutate. Therefore, at this time, FDA believes that whole genome sequencing tests may be best suited for genotyping claims due to their ability to detect both known and emerging mutations and variants. FDA recommends that developers of sequencing tests pursuing an EUA with a genotyping claim engage in early discussions with FDA.[13]

1. Design Considerations to Minimize Impact of Viral Mutations

For molecular tests, FDA recommends developers consider the performance of their test across all known variants at the time of validation and the potential impact of future genetic variants when considering their test design. Designing redundancy into a test may prevent future variants from impacting test performance. Tests with multiple targets and appropriate result interpretation criteria have been used to identify signals that a patient sample may include a variant and should be followed up with additional testing and/or sequencing of the viral genome.[14]

FDA recommends that test developers include in their EUA request a description of how they have evaluated their test performance across all known variants having mutations in the targeted region and a discussion of how their test design mitigates the risk of future viral mutations impacting the

[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-revised
[12] https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests
[13] Developers may discuss their genotyping tests with FDA through COVID19Dx@FDA.HHS.GOV.
[14] https://www.cdc.gov/mmwr/volumes/70/wr/mm7003e2.htm?s_cid=mm7003e2_w

test performance.

Including a highly conserved pan-SARS-CoV target (a target in a portion of the genetic code associated with the larger Sarbecovirus subgenus of the genus Betacoronavirus in the Coronaviridae family not specific to SARS-CoV-2) as part of a multiple target test may improve performance with a new genetic variant; however, the number of targets in the test should be appropriate to provide resilience (i.e., a reduction of the risk that viral mutation will impact test performance) and most efficiently leverage developer and laboratory resources. When using a highly conserved target in combination with SARS-CoV-2 specific targets, appropriate result interpretation, such as how to interpret results when a pan-SARS-CoV target is positive while the SARS-CoV-2 specific targets are not and follow-up recommendations for an overall positive result with individual gene negative results, may be needed.

2. Routine Monitoring of Viral Mutations that May Impact Molecular Diagnostic Test Performance

Test developers should assess the potential impact of variants and mutations observed at a significant frequency on their molecular diagnostic test, as well as the potential impact of those viral mutations detected in a smaller percent of the population where there are signs of increasing prevalence.

In particular, FDA suggests that developers of molecular tests should periodically conduct sequence alignment of their primer/probe sequences with publicly available SARS-CoV-2 genomes, such as in the GISAID database, to determine the extent to which mutations may impact test performance. If any mutations are identified in the target regions of the test's primers and probes (or equivalent if the test uses an alternative amplification approach), the developer should consider several factors: (1) location of the sequence mismatch within the primers/probes, (2) whether multiple sequence mismatches could impact a single test, and (3) whether the aggregate of mutations could impact a particular test to reduce performance by 5% or more from the previously established performance (as reflected in the authorization documents for authorized tests), or drop the test's performance below the performance recommendations in the applicable EUA template(s) for molecular diagnostic tests for SARS-CoV-2 as discussed in Section VI of FDA's guidance Policy for Coronavirus Disease-2019 Tests (Revised).[15] The EUA templates include information and recommendations for monitoring sequence databases and FDA intends to update the EUA template(s) as databases are improved and a more systematic collection of viral sequences becomes available.

Since mutations in the viral genome can affect hybridization of test reagents with SARS-CoV-2, FDA recommends evaluating hybridization changes when a test developer identifies a mutation expected to result in a mismatch, or mismatches, within the target primer/probe binding site(s). Investigations of the impact on hybridization can be done in three stages, each providing a more accurate evaluation of test performance than the last: *in silico* calculation, wet testing of genomic material, and wet testing of a virus isolate with a mutation. FDA recommends that the developer investigate the impact that the corresponding viral mutation may confer on test performance and provide FDA with the following information in their EUA request (if conducted pre-EUA) or in a

[15] These templates are also available on FDA's website at https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas#covid19ivdTemplates.

supplemental EUA request (if conducted post-EUA):

1) The results from melting temperature (T_m) calculations with the test's primers and/or probes and the viral target with and without the mutation(s) in question. T_m is a calculation which provides information on the hybridization of DNA or RNA. When a mutation is introduced into a sequence, the T_m can decrease if the stability of the DNA/DNA or DNA/RNA duplex has been reduced. FDA recommends performing this calculation using conditions such as ion concentration and primer excess which are reflective of the conditions of the test. FDA recommends providing a description of the method used to calculate T_m.

2) An analysis to establish how the melting temperature changes as a function of changing salt and primer concentration.

3) An analysis and justification of the likelihood that the mutation may impact test performance and an evaluation of the impact on the benefits and risks of the test; and

4) A justification for any actions taken, or not taken, based on the outcome of the developer's analysis.

Based on the results of the analysis, the developer should determine whether the mutation in question has a significant likelihood to impact the performance of their test, such as a reduction in T_m to at or below the annealing temperature of the test, or a mutation associated with known or suspected false negatives suggesting a reduction in the test's performance below the performance recommendations in the applicable EUA template(s).[16] If it does, FDA recommends wet testing with a clinical sample with the mutation, if available. If not available, due to potential difficulties in identifying and acquiring such a sample, FDA recommends using synthetic RNA targets with and without the mutation. Testing should be performed in a manner similar to a typical limit of detection (LoD) study where limiting dilutions are tested in parallel and the LoD is established for both synthetic targets.

If a difference of $\geq$3-fold in LoD is found, and the test is not yet authorized, FDA recommends that the developer's EUA request include a risk analysis for the observed decrease in performance and either a description and justification of any further risk mitigations, or alternatively, if the developer believes that no mitigations are needed, a justification for the position that the known and potential benefits outweigh the known and potential risks.

For already authorized tests, if a difference of $\geq$3-fold in LoD is found or the test developer otherwise identifies viral mutations with the potential to change the benefit-risk profile of their product, it is FDA's current recommendation that test developers notify FDA in a supplemental EUA request including a risk analysis for the observed decrease in sensitivity and either a description and justification of any further risk mitigations, or alternatively, if the developer believes that no mitigations are needed, a justification for the position that the known and potential benefits outweigh the known and potential risks.

[16] These templates are also available on FDA's website at https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas#covid19ivdTemplates.

If requested by FDA, test developers should submit records of the recommended evaluations to FDA for review in a timely manner. FDA may request additional studies and/or data analysis to address concerns identified by a test developer or by FDA (e.g., through FDA's monitoring program).

If requested by FDA to evaluate the impact of a specific mutation(s) or variant(s), FDA expects a test developer of an authorized test to perform the requested evaluation in a timely manner. FDA expects that such studies, study designs and/or data analysis, including a timeline for submission of information to FDA, will be agreed upon between a test developer and FDA. For instance, FDA may request to establish the LoD using limiting dilutions of quantified synthetic RNA or quantified in vitro transcripts of both the target sequence from the reference genome (i.e., perfect match target) and the sequence harboring the mutation of interest.

Further, if FDA identifies signals concerning authorized molecular diagnostic tests through our monitoring efforts, FDA will contact the test developer and expects the developer to investigate the impact that the viral genome mutation identified may confer to the performance of its test and provide information from that investigation back to FDA in a timely manner.

If a potential impact on performance of an authorized test is identified, FDA intends to work with the test developer to address those issues, for example by updating their labeling to reflect potential changes in performance of their test, or to consider modifications to the test if needed. FDA may also take additional actions, such as revocation of an EUA, as appropriate.

B. Recommendations for Antigen Diagnostic Tests and Serology Tests

FDA also recommends that developers of antigen diagnostic tests and serology tests consider the potential for future genetic mutations and viral variants when developing their test. Monitoring the impact of genetic variants on antigen tests and serology tests is not as straightforward as for molecular tests. FDA is considering how to best assess the impact on antigen and serology test performance, such as obtaining samples of novel variants to characterize their impact on the analytical performance of the test, using in silico and/or in vitro models to characterize the impact of certain mutations on the proteins responsible for eliciting an antibody response, and/or evaluating the clinical performance using clinical specimens obtained from individuals with the novel viral variants.

Test developers should engage in discussions with FDA early during their test development to ensure they are apprised of any new developments as FDA continues to develop appropriate recommendations for approaches that test developers could use to evaluate the impact of novel variants on the performance of antigen tests and serology tests, including those already authorized and those for which the test developers are seeking or will seek an EUA or marketing authorization or clearance.

Test developers should consider the potential impact of genetic mutations and variants already in circulation and develop a plan to 1) routinely monitor for new genetic mutations and viral variants and 2) assess the impact of the mutations or viral variants on their test's performance, as needed, considering the potential of a given mutation or viral variant to impact their test.

Test developers, both pre- and post-authorization, should also consider whether there is the potential for the aggregate of mutations to reduce performance of the test by 5% or more from the previously established performance (as reflected in the authorization documents for authorized tests), or to drop the test's performance below the performance recommendations in the applicable EUA template.[17]

FDA intends to update the EUA templates[18] with additional considerations related to the impact of genetic variants on test performance as we learn more about the COVID-19 disease and our knowledge in this area progresses.

V. Additional Resources for Test Developers

The following resources may be useful to developers for monitoring genetic variants and the potential impact on test performance:

- GISAID is a global science initiative and primary source that provides open-access to genomic data of influenza viruses and the novel coronavirus responsible for COVID-19. https://www.gisaid.org/

- FDA COVID-19 Test Policy Guidance: *Policy for Coronavirus Disease-2019 Tests (Revised) - Guidance for Developers and Food and Drug Administration Staff*

- FDA EUA Templates that developers may choose to use to facilitate the preparation, submission, and authorization of an EUA for various types of COVID-19 tests. These templates are part of the *Policy for Coronavirus Disease-2019 Tests (Revised) - Guidance for Developers and Food and Drug Administration Staff*, which also includes additional policies specific to this public health emergency. The templates reflect FDA's current thinking on the data and information that developers should submit to facilitate the EUA process. The templates provide information and recommendations, and we plan to update them as appropriate as we learn more about the COVID-19 disease and gain experience with the EUA process for the various types of COVID-19 tests. FDA EUA templates are also available on FDA's website at https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas#covid19ivdTemplates

- FDA FAQs on Testing for SARS-CoV-2: https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2

- CDC Summary of Variant Surveillance: https://covid.cdc.gov/covid-data-tracker/#variant-summary

[17] https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas#covid19ivdTemplates
[18] https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas#covid19ivdTemplates

- CDC SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance: https://www.cdc.gov/coronavirus/2019-ncov/variants/spheres.html
- WHO SARS-CoV-2 Variants: https://www.who.int/activities/tracking-SARS-CoV-2-variants

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