Medicines & Healthcare products
Regulatory Agency

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Important safety information - bimonthly voluntary *in silico* submissions

Re: Impact of SARS-CoV-2 variants on the performance of diagnostic and screening assays.

This letter is relevant for manufacturers of SARS-CoV-2 diagnostic and screening assays and clarifies expectations for manufacturers.

The MHRA are working with government partners to provide an assurance framework and monitor the potential impact of Variants of Concern (VOC) and Variants under Investigation (VUI) on diagnostic assay performance.

Variants have the potential to impact test performance of diagnostic assays which may use affected gene regions. Action is required by manufacturers regardless of the diagnostic assay targets. Please refer to the following link for continually updated SARS-CoV-2 lineage prevalence and growth rates: SARS-CoV-2: genome sequence prevalence and growth rate - GOV.UK (www.gov.uk).

Pathogen Diagnostic Assurance Group recommendations

The VOC assurance working group has been renamed the Pathogen Diagnostic Assurance Group (PDAG), and is a collaboration of the MHRA with UKHSA, NHS, COG-UK, RCpath and partners in the devolved administrations. One function of this group is to review the feedback from manufacturers and the results of variant *in vitro* testing performed in UK clinical diagnostic laboratories.
The attached document titled “Antigen assay guidance for SARS-CoV-2 variant analysis” has been produced to clarify the minimum dataset requirements for *in silico* analysis of diagnostic assay performance. Following CTDA approval, manufacturers are encouraged to follow these recommendations and respond to the MHRA regarding the following actions.

ACTIONS FOR MANUFACTURERS: Bimonthly updates (due the second week of every other month) *

In line with UK MDR 2002 vigilance and field safety corrective action reporting requirements, the MHRA consider reports relating to assays affected by VOCs to be serious public health threats, therefore significant safety issues should be reported within 48 hours.

1) A Post Market Surveillance Plan (PMSP) should be in place to continuously monitor, investigate and assess newly emerging variants of SARS-CoV-2. The PMSP can include:
    a. 60 day *in silico* checks of assay targets against GISAID sequence databases (https://www.gisaid.org) [Please note that high profile potential issues should be immediately investigated]
    b. Scientific literature and post market intelligence gathering
    c. Outcomes of EQA schemes when available
    d. Use of reference materials when available
    e. Reporting potential safety issues of any new clinically significant variant SARS-CoV-2 strain on the performance of your assay to the MHRA

2) In your response to this letter, please include the following information with regards to the variants highlighted above:
    a. The outcome of the initial risk assessment of any impact on each primer/probe/other oligonucleotide target sequence and on the performance of the assay in light of all variants
    b. Clarification on whether the sensitivity of any gene targets in the diagnostic assay is affected by any of the variants
    c. Clarification on whether each of the identified variants can be detected by your assay
    d. Type of *in silico* analysis performed
    e. All identifiers of the sequences used in the analysis (for example, COG-UK ID or accession) and sequence selection criteria to ensure that the data used can be independently identified if required
    f. Frequency of mutations
    g. Clarification on whether wet testing will be carried out in light of the VOC

3) Please also provide your plan to mitigate against any new risks from mutations, including your timelines for addressing these.

** Please refer to the Excel attachment for the proforma which should be completed with this information.*

It is required that both favourable and unfavourable data are reported to the MHRA as assurance of either positive or negative performance.

If the performance of any of your assay targets, including each oligonucleotide target sequence, is directly impacted by these new virus variant(s), a Field Safety Notice should be issued immediately to alert customers. Further guidance on effective FSNs can be found here.

If *in silico* analysis is not performed for any reason, manufacturers are recommended to provide the MHRA with their assay sequences. This information will not be made public, and any mismatches will be reported directly to the manufacturer.

Further information can be found on our webpage “Guidance for manufacturers diagnostic assurance with SARS-CoV-2 variants in circulation”.

Responses to be sent to COVID19.variants@mhra.gov.uk. Bimonthly updates should be sent to the same address on the second week of every two months, and the email subject should be in the following format “[company name] [month] [pathogen] VOC assurance update - antigen assay”.

If you have any queries about this letter, please contact us using the email address above.

Safety and Surveillance Group
MHRA