May 10, 2024

QIAGEN GmbH
% Melissa Mahall
Senior Director, Regulatory Affairs
Qiagen
19300 Germantown Road
Germantown, Maryland 20874

Re: K233100
Trade/Device Name: QIAstat-Dx Respiratory Panel Plus
Regulation Number: 21 CFR 866.3981
Regulation Name: Device 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
Regulatory Class: Class II
Product Code: QOF
Dated: September 26, 2023
Received: September 26, 2023

Dear Melissa Mahall:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Joseph Briggs -S

Joseph Briggs, Ph.D.
Deputy Branch Chief
Viral Respiratory and HPV Branch
Division of Microbiology Devices

OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 07/31/2026
See PRA Statement below.

510(k) Number *(if known)*
K233100

Device Name
QIAstat-Dx® Respiratory Panel Plus

Indications for Use *(Describe)*
The QIAstat-Dx Respiratory Panel Plus is a multiplexed nucleic acid test intended for use with the QIAstat-Dx system for the simultaneous in vitro qualitative detection and identification of multiple respiratory viral and bacterial nucleic acids in nasopharyngeal swabs (NPS) obtained from individuals with clinical signs and symptoms of respiratory tract infection, including SARS-CoV-2.

The following organism types and subtypes are identified using the QIAstat-Dx Respiratory Panel Plus: Adenovirus, Human Coronavirus 229E, Human Coronavirus HKU1, Human Coronavirus NL63, Human Coronavirus OC43, Human Metapneumovirus, Influenza A, Influenza A H1, Influenza A H1N1 pdm09, Influenza A H3, Influenza B, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Respiratory Syncytial Virus, Human Rhinovirus/Enterovirus (not differentiated), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), Bordetella pertussis, Chlamydophila pneumoniae and Mycoplasma pneumoniae.

Nucleic acids from viral and bacterial organisms identified by this test are generally detectable in NPS specimens during the acute phase of infection. Detecting and identifying specific viral and bacterial nucleic acids from individuals presenting with signs and symptoms of a respiratory infection aids in the diagnosis of respiratory infection, if used in conjunction with other clinical, epidemiological and laboratory findings. The results of this test should not be used as the sole basis for diagnosis, treatment or other patient management decisions.

Negative results in the presence of a respiratory illness may be due to infection with pathogens that are not detected by the test or due to lower respiratory tract infection that is not detected by a NPS specimen.

Conversely, positive results are indicative of the presence of the identified microorganism, but do not rule out co-infection with other pathogens not detected by the QIAstat-Dx Respiratory Panel Plus. The agent(s) detected by the QIAstat-Dx Respiratory Panel Plus may not be the definite cause of disease.

The use of additional laboratory testing (e.g., bacterial and viral culture, immunofluorescence and radiography) may be necessary when evaluating a patient with possible respiratory tract infection.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

General Information

Submitted by: QIAGEN GmbH
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Date Prepared: May 08, 2024

Device Name: QIAstat-Dx Respiratory Panel Plus

Classification: 21 CFR 866.3981 - Device 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

Product Code: QOF

Predicate Device:

Manufacturer	**Product Name**	**De Novo/510(k) No.**
BioFire Diagnostics, LLC	BioFire Respiratory Panel 2.1 (RP2.1)	DEN200031

Device Description

The QIAstat-Dx Respiratory Panel Plus is part of the QIAstat-Dx system and works with the QIAstat-Dx Analyzer 1.0.

The QIAstat-Dx Respiratory Panel Plus is intended to be used with l nasopharyngeal swab (NPS) eluted in Universal Transport Media (UTM), which is not provided with the QIAstat-Dx Respiratory Panel Plus.

Once the cartridge has been inserted into the instrument, the test starts automatically and runs for approximately 1 hour. When the test is finished, the cartridge is removed by the user and discarded. The QIAstat-Dx Analyzer 1.0 automatically interprets test results and displays a summary on the analyzer display screen. The results can be printed using a connected printer if needed. The detected analytes are displayed in red. All other tested but not detected analytes are listed in green. The analyzer will report if an error occurs during processing, in which case the test will fail and no results will be provided (screen will show "FAIL").

All the reagents required for the complete execution of the test are pre-loaded and self-contained in the QIAstat-Dx Respiratory Panel Plus cartridge. The user does not need to manipulate any reagents. During the test, reagents are handled by pneumatically-operated microfluidics without any direct contact with the user or the analyzer actuators.

Within the cartridge, multiple steps are automatically performed in sequence by using pneumatic pressure and a multiport valve to transfer sample and fluids via the Transfer Chamber (TC) to their intended destinations. Following the introduction of the sample from a disposable transfer pipette, the following assay steps occur automatically and sequentially:

- Resuspension of air-dried internal control and Proteinase K (ProtK) enzyme using provided buffer and mixing with the liquid sample (IC Cavity and ProtK Cavity);
- Cell lysis using mechanical (rotation) and chemical (chaotropic and isotonic) means (lysis chamber);
- Membrane based nucleic acid purification from Lysate by:
    - Mixing lysate with binding buffer and capturing on the membrane (purification chamber);
    - First washing of membrane to remove bound proteins (purification chamber and waste chamber);
    - Second washing of membrane to leave only bound nucleic acids (purification chamber and waste chamber);
    - Rinsing of Transfer Chamber (TC) using the rinsing buffer before introduction of the eluate (Transfer Chamber);
    - Drying of membrane with bound nucleic acids with an air flow generated by a high flow vacuum pump (purification chamber);
    - Elution of nucleic acids with elution buffer (purification chamber and TC);

- Mixing of the purified nucleic acid (eluate) with lyophilized "Master Mix" reagents (Dry chemistry container (DCC) and TC);
- Sequential transfer of defined aliquots of mixed eluate/Master Mix from the Transfer Chamber to each of eight Reaction Chambers containing the specified, air-dried primers and probes;
- Within each Reaction Chamber, real-time, multiplex PCR ("rtPCR") testing is performed. Increase in fluorescence (indicative of detection of each target analyte) is detected directly within each Reaction Chamber;
- The detected signal per fluorescent marker per Reaction Chamber is then used by the system software to generate the assay result.

The QIAstat-Dx Respiratory Panel Plus includes the addition of the SARS-CoV-2 analyte to the analytes that were cleared in the QIAstat-Dx Respiratory Panel (K183597).

Intended Use

The QIAstat-Dx Respiratory Panel Plus is a multiplexed nucleic acid test intended for use with the QIAstat-Dx system for the simultaneous *in vitro* qualitative detection and identification of multiple respiratory viral and bacterial nucleic acids in nasopharyngeal swabs (NPS) obtained from individuals with clinical signs and symptoms of respiratory tract infection, including SARS-CoV-2.

The following organism types and subtypes are identified using the QIAstat-Dx Respiratory Panel Plus: Adenovirus, Human Coronavirus 229E, Human Coronavirus HKU1, Human Coronavirus NL63, Human Coronavirus OC43, Human Metapneumovirus, Influenza A, Influenza A H1, Influenza A H1N1 pdm09, Influenza A H3, Influenza B, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Respiratory Syncytial Virus, Human Rhinovirus/Enterovirus (not differentiated), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), *Bordetella pertussis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.

Nucleic acids from viral and bacterial organisms identified by this test are generally detectable in NPS specimens during the acute phase of infection. Detecting and identifying specific viral and bacterial nucleic acids from individuals presenting with signs and symptoms of a respiratory infection aids in the diagnosis of respiratory infection, if used in conjunction with other clinical, epidemiological and laboratory findings. The results of this test should not be used as the sole basis for diagnosis, treatment or other patient management decisions.

Negative results in the presence of a respiratory illness may be due to infection with pathogens that are not detected by the test or due to lower respiratory tract infection that is not detected by a NPS specimen.

Conversely, positive results are indicative of the presence of the identified microorganism, but do not rule out co-infection with other pathogens not detected by the QIAstat-Dx

Respiratory Panel Plus. The agent(s) detected by the QIAstat-Dx Respiratory Panel Plus may not be the definite cause of disease.

The use of additional laboratory testing (e.g., bacterial and viral culture, immunofluorescence and radiography) may be necessary when evaluating a patient with possible respiratory tract infection.

Comparison of the QIAstat-Dx Respiratory Panel Plus and the Predicate Device

Similarities and differences between the QIAstat-Dx Respiratory Panel Plus and the predicate device are shown in Table 5.1.

Table 5.1: Comparison of the QIAstat-Dx Respiratory Panel Plus with the predicate device

Characteristic	Subject Device	Predicate
Name	QIAstat-Dx Respiratory Panel Plus	BioFire Respiratory Panel 2.1 (RP2.1)
De Novo/510(k) No.	K233100	DEN200031
Regulation	21 CFR 866.3981	21 CFR 866.3981
Product Code	QOF	QOF
Device Class	Class II	Class II
Similarities		
Intended Use	The QIAstat-Dx Respiratory Panel Plus is a multiplexed nucleic acid test intended for use with the QIAstat-Dx system for the simultaneous *in vitro* qualitative detection and identification of multiple respiratory viral and bacterial nucleic acids in nasopharyngeal swabs (NPS) obtained from individuals with clinical signs and symptoms of respiratory tract infection, including SARS-CoV-2. The following organism types and subtypes are identified using the QIAstat-Dx Respiratory Panel Plus: Adenovirus, Human Coronavirus 229E, Human Coronavirus HKU1, Human	The BioFire Respiratory Panel 2.1 (RP2.1) is a PCR-based multiplexed nucleic acid test intended for use with the BioFire FilmArray 2.0 or BioFire FilmArray Torch systems for the simultaneous qualitative detection and identification of multiple respiratory viral and bacterial nucleic acids in nasopharyngeal swabs (NPS) obtained from individuals suspected of respiratory tract infections, including COVID-19. The following organism types and subtypes are identified using the BioFire RP2.1: • Adenovirus, • Coronavirus 229E, • Coronavirus HKU1,

Characteristic	Subject Device	Predicate
	Coronavirus NL63, Human Coronavirus OC43, Human Metapneumovirus, Influenza A, Influenza A H1, Influenza A H1N1 pdm09, Influenza A H3, Influenza B, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Respiratory Syncytial Virus, Human Rhinovirus/Enterovirus (not differentiated), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), *Bordetella pertussis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*. Nucleic acids from viral and bacterial organisms identified by this test are generally detectable in NPS specimens during the acute phase of infection. Detecting and identifying specific viral and bacterial nucleic acids from individuals presenting with signs and symptoms of a respiratory infection aids in the diagnosis of respiratory infection, if used in conjunction with other clinical, epidemiological and laboratory findings. The results of this test should not be used as the sole basis for diagnosis, treatment or other patient management decisions. Negative results in the presence of a respiratory illness may be due to infection with pathogens that are not detected by the test or due to lower respiratory tract	• Coronavirus NL63, • Coronavirus OC43, • Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), • Human Metapneumovirus, • Human Rhinovirus/Enterovirus, • Influenza A, including subtypes H1, H1-2009, and H3, • Influenza B, • Parainfluenza Virus 1, • Parainfluenza Virus 2, • Parainfluenza Virus 3, • Parainfluenza Virus 4, • Respiratory Syncytial Virus, • *Bordetella parapertussis* (IS1001), • *Bordetella pertussis* (ptxP), • *Chlamydia pneumoniae*, and • *Mycoplasma pneumoniae* Nucleic acids from the respiratory viral and bacterial organisms identified by this test are generally detectable in NPS specimens during the acute phase of infection. The detection and identification of specific viral and bacterial nucleic acids from individuals exhibiting signs and/or symptoms of respiratory infection is indicative of the presence of the identified microorganism and aids in the diagnosis of respiratory infection if used in conjunction with other

Characteristic	Subject Device	Predicate
	infection that is not detected by a NPS specimen. Conversely, positive results are indicative of the presence of the identified microorganism, but do not rule out co-infection with other pathogens not detected by the QIAstat-Dx Respiratory Panel Plus. The agent(s) detected by the QIAstat-Dx Respiratory Panel Plus may not be the definite cause of disease. The use of additional laboratory testing (e.g., bacterial and viral culture, immunofluorescence and radiography) may be necessary when evaluating a patient with possible respiratory tract infection.	clinical and epidemiological information. The results of this test should not be used as the sole basis for diagnosis, treatment, or other patient management decisions. Negative results in the setting of a respiratory illness may be due to infection with pathogens that are not detected by this test, or lower respiratory tract infection that may not be detected by an NPS specimen. Positive results do not rule out coinfection with other organisms. The agent(s) detected by the BioFire RP2.1 may not be the definite cause of disease. Additional laboratory testing (e.g. bacterial and viral culture, immunofluorescence, and radiography) may be necessary when evaluating a patient with possible respiratory tract infection.
Specimen Type	Nasopharyngeal swabs (NPS)	Nasopharyngeal swabs (NPS)
Organism Detected	See analyte list above, RNA/DNA	See analyte list above, RNA/DNA
Amplification and Detection Technology	PCR	PCR

Characteristic	Subject Device	Predicate
Assay Controls	One internal control in each cartridge to control for sample processing that is subjected to all nucleic acid extraction and amplification steps similar to patient samples. Instructions for Use indicates quality control requirements should be performed in conformance with local, state, and/or federal regulations or accreditation requirements and the laboratory's standard quality control procedures.	Two controls are included in each reagent pouch to control for sample processing and both stages of PCR and melt analysis. Labeling recommends the use of external positive and negative controls regularly. Use viral transport medium as the external negative control, and previously characterized positive samples or negative samples spiked with well characterized organisms as external positive controls.
Differences		
Characteristic	**Subject Device**	**Predicate**
Bordetella Assay Targets	The QIAstat-Dx Respiratory Panel Plus detects *Bordetella pertussis*.	The BioFire Respiratory Panel 2.1 (RP2.1) detects *Bordetella pertussis* (ptxP) and *Bordetella parapertussis* (IS1001).
Nucleic Acid Extraction	Extraction of nucleic acids using spin columns	Extraction of nucleic acids using magnetic beads
Detection Technology	Detection of amplified targets uses an increase in fluorescence to generate the assay results.	Melting curve analysis is used to confirm the identity of amplified targets to generate assay results.
Operational	The sample is loaded straight into the cartridge.	The pouch is hydrated prior to introducing the sample.
Amplification and Detection Instrument System	QIAstat-Dx Analyzer 1.0	FilmArray 2.0 or FilmArray Torch systems

Performance Characteristics - Clinical Studies

SARS-CoV-2

The clinical performance of the SARS-CoV-2 target in the QIAstat-Dx Respiratory Panel Plus was established through studies conducted at five (5) geographically diverse study sites in the U.S. The sites were representative of testing environments where the device will ultimately be used. The testing was performed by laboratory personnel likely to perform the testing in clinical practice after device marketing. Nasopharyngeal swab (NPS) specimens were prospectively collected from patients with signs and symptoms of respiratory infection.

A total of 616 prospective NPS specimens in UTM were enrolled and tested in a comparison study. One specimen was excluded due to not meeting the inclusion criteria, so 615 specimens were included in the analysis. From February 2023 to May 2023 and during February 2024, NPS specimens were prospectively collected from individuals meeting the study inclusion criteria. NPS specimens were tested fresh on both the QIAstat-Dx Respiratory Panel Plus and an FDA-cleared SARS-CoV-2 RT-PCR comparator method.

The performance of the SARS-CoV-2 target in the QIAstat-Dx Respiratory Panel Plus was evaluated by comparing the SARS-CoV-2 QIAstat-Dx Respiratory Panel Plus result with the result from an FDA-cleared SARS-CoV-2 RT-PCR comparator method. The SARS-CoV-2 QIAstat-Dx Respiratory Panel Plus prospective performance data in positive percent and negative percent agreements against the comparator method are presented in Table 5.2.

Table 5.2: QIAstat-Dx Respiratory Panel Plus SARS-CoV-2 prospective clinical performance summary

	Positive Percent Agreement			Negative Percent Agreement		
Target	**TP/(TP+FN)**	**%**	**95% CI**	**TN/(TN+FP)**	**%**	**95% CI**
SARS-CoV-2	61 / 63[1]	96.8%	89.0%-99.6%	551 / 552[2]	99.8%	99.0%-100.0%

TP-True Positive, FP-False Positive, TN-True Negative, FN-False Negative

[1]The two samples with false negative SARS-CoV-2 results by the QIAstat-Dx Respiratory Panel Plus were both positive by two FDA-EUA molecular SARS-CoV-2 assays.

[2]The single sample with a false positive SARS-CoV-2 result by the QIAstat-Dx Respiratory Panel Plus was positive by two FDA-EUA molecular SARS-CoV-2 assays.

There were two specimens that yielded a co-infection including SARS-CoV-2 by the QIAstat-Dx Respiratory Panel Plus. One was positive for Human Metapneumovirus and the second was positive for Rhinovirus/Enterovirus. Both results were true positive based on the comparator result.

Representative Panel Equivalency

Clinical performance for the non-SARS-CoV-2 analytes were established previously in K183597. To confirm the clinical performance of the original panel analytes and to demonstrate clinical performance equivalence between the two products (the previously cleared QIAstat-Dx Respiratory Panel in K183597 and QIAstat-Dx Respiratory Panel Plus) a subset of original panel analytes were chosen as a representative panel for an internal comparison study. The representative panel covers all target types (RNA, DNA, Bacteria, Viral), one target from each Reaction Chamber within the test cartridge and was chosen based on the prevalence of the pathogen, including:

1. Influenza B
2. Coronavirus OC43
3. Parainfluenza virus 3
4. Rhinovirus/enterovirus
5. Adenovirus
6. *Bordetella pertussis*

A total of 190 de-identified clinical NPS specimens, both positive and negative as per Standard of Care, were obtained and tested for the representative panel analytes. Each specimen was run in parallel on QIAstat-Dx Respiratory Panel and QIAstat-Dx Respiratory Panel Plus. The performance data in positive percent and negative percent agreements are summarized in Table 5.3.

Table 5.3: PPA and NPA of the Representative Panel analytes between QIAstat-Dx Respiratory Panel Plus and QIAstat-Dx Respiratory Panel

Grouping Variable(s)		Proportion[a]		Two-Sided 95% Confidence Limit	
Analysis	**Pathogen**	**Fraction**	**Percentage**	**Lower**	**Upper**
PPA	Influenza B	20 / 20	100.0%	83.2%	100.0%
	Coronavirus OC43	22 / 22	100.0%	84.6%	100.0%
	Parainfluenza virus 3	24 / 24	100.0%	85.8%	100.0%
	Rhinovirus / Enterovirus	43 / 43	100.0%	91.8%	100.0%
	Adenovirus	38 / 40	95.0%	83.1%	99.4%
	Bordetella pertussis	24 / 24	100.0%	85.8%	100.0%
NPA	Influenza B	167 / 168	99.4%	96.7%	100.0%
	Coronavirus OC43	166 / 166	100.0%	97.8%	100.0%
	Parainfluenza virus 3	163 / 164	99.4%	96.7%	100.0%
	Rhinovirus / Enterovirus	144 / 145	99.3%	96.2%	100.0%
	Adenovirus	144 / 148	97.3%	93.2%	99.3%
	Bordetella pertussis	163 / 164	99.4%	96.7%	100.0%

[a] The performance of the QIAstat-Dx Respiratory Panel Plus was established by comparing to results from the QIAstat-Dx Respiratory Panel.

Clinical performance equivalence between the two products (QIAstat-Dx Respiratory Panel and QIAstat-Dx Respiratory Panel Plus) has been demonstrated showing that the addition of SARS-CoV-2 and change in the lysis reagent had no impact to the performance of the original panel analytes.

Performance Characteristics - Non-clinical Studies

The studies presented have been performed to demonstrate the non-clinical performance of the SARS-CoV-2 assay. In addition, where indicated, a subset of original panel analytes were tested to demonstrate the addition of SARS-CoV-2 and change in the lysis reagent does not impact the performance of the original panel analytes. The performance of the original panel analytes is described in K183597.

Limit of Detection

The Limit of Detection (LoD) is defined as the lowest concentration at which ≥95% of the tested sample generates a positive call. A total of 5 SARS-CoV-2 strains were evaluated in the LoD study by analyzing serial dilutions of contrived samples prepared from culture isolates obtained from commercial suppliers or clinical samples positive for the target analyte. Samples were prepared by spiking SARS-CoV-2 into NPS matrix. The concentration estimated to be the LoD was confirmed by testing 20 replicates during at least 3 different days by different operators using at least four different lots of QIAstat-Dx Respiratory Panel Plus cartridges executed on 3 or more QIAstat-Dx Analyzer 1.0 instruments.

Individual LoD concentrations for each SARS-CoV-2 strain is shown in Table 5.4.

Table 5.4: LoD concentrations for SARS-CoV-2 strains tested with QIAstat-Dx Respiratory Panel Plus

Pathogen	Source/ Catalog ID	Strain	LoD concentration (copies/mL[a])	Detection rate
SARS-CoV-2	ZeptoMetrix/ 0810587CFH	USA-WA1-2020	3160.0	19/20
SARS-CoV-2	NIBSC/ First WHO International Standard for SARS-CoV-2 RNA 20/146	England/02/2020	316.0	19/20
SARS-CoV-2	STAT-Dx Life, S.L. – Clinical sample/ 243	n/a	600.0	20/20
SARS-CoV-2	Vall d'Hebron hospital – Clinical sample/ S1229	n/a	1.90E+04	20/20
SARS-CoV-2	Vall d'Hebron hospital – Clinical sample/ S1231	n/a	1.90E+04	20/20

[a] Titer determined in molecular units (copies/mL) by in-house developed and validated qPCR assay.

LoD and equivalency for the previously cleared QIAstat-Dx Respiratory Panel cartridges and the new QIAstat-Dx Respiratory Panel Plus cartridges were confirmed by testing a subset of original panel analytes. Testing consisted of twenty replicates tested side-by-side on the cleared device and the new device containing SARS-CoV-2 at the LoD concentration as defined for the cleared device (QIAstat-Dx Respiratory Panel) verifying that the addition of the SARS-CoV-2 assay and change in the lysis reagent does not impact the performance of targets in other reaction chambers.

Analytical Reactivity (Inclusivity)

QIAGEN routinely evaluates the overall inclusivity of the entire set of SARS-CoV-2 available genomes, including all relevant variants and lineages. This includes (1) Inclusivity Analysis and mismatch detection among SARS-CoV-2 strains and (2) same analysis focused on specific SARS-CoV-2 variants or lineages, evaluating the possible effect of detected mismatches in the QIAstat-Dx performance. Only critical mismatches established were evaluated in the laboratory.

In total, 8,118,241 available genomes since 01.01.2020 until 06.05.2022 from around the globe were analyzed for inclusivity (additional vigilance of SARS-CoV-2 genomic variability is continuously done internally in the Post-Market Surveillance QIAGEN monitoring study). Of them, 7,932,071 (97.71%) presented no evidence of mismatches in the targeted regions. The remainder of genomes (2.01%) presented any mismatch among the sequence in the binding region, but only 19,045 (0.23%) presented a mismatch (3'-end of any primer) in a critical position and frequency >0.2%. Genetic patterns included among those sequences were evaluated in laboratory testing, with no loss of performance at LoD level. Consequently, 100% of sequences analyzed were predicted to be detected.

Variants of Concern, of Interest and Under Investigation (VOCs, VOIs, VUI respectively) were also evaluated from the 8,118,241 sequences. After classifying all previously analyzed genomes into lineages based on GISAID and PANGO classifications, the following variants were included: Alpha (9 clades), Beta (5 clades), Gamma (23 clades), Lambda (2 clades), Mu (4 clades), Delta (242 clades), Omicron (73 clades). As a result, all variants and lineages described are 100% predicted to be detected.

For the rest of the analytes detected by the QIAstat-Dx Respiratory Panel Plus, an updated *in silico* analysis was performed to confirm previous device inclusivity results. All single primers and probes corresponding to targets included in the QIAstat-Dx Respiratory Panel Plus (non-SARS-CoV-2 targets) were analyzed to detect the specificity of the Panel using BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

All QIAstat-Dx Respiratory Panel Plus primers and probes are predicted to be inclusive for all clinical prevalent and relevant strains for each pathogen against all available sequences in the NCBI data base.

Analytical Specificity (Exclusivity)

The potential for cross-reactivity between all QIAstat-Dx Respiratory Panel Plus on-panel organisms (including SARS-CoV-2) and various on-panel or off-panel organisms that can happen in clinical respiratory specimens was evaluated with a combination of laboratory (*in vitro*) testing and *in silico* characterization. For laboratory testing, on-panel (intra-panel cross-reactivity) and off-panel tested organisms (not covered by the panel content and, therefore, not intended to be detected by the QIAstat-Dx Respiratory Panel Plus) complement the organisms evaluated in the previously cleared device (QIAstat-Dx Respiratory Panel) and add additional organisms selected to assess the specificity of the

new SARS-CoV-2 assays included in the Panel. Additionally, all single primers and probes for the SARS-CoV-2 detection were analyzed *in silico* to complement the overall specificity prediction of the device. On-panel organisms were tested to assess the potential for intra-panel cross-reactivity and off-panel organisms were tested to evaluate panel exclusivity. These organisms included those which are related to, but distinct from, respiratory panel organisms or that could be present in specimens collected from the intended test population. Selected organisms are clinically relevant (colonizing the upper respiratory tract or causing respiratory symptoms), are common skin flora or laboratory contaminants, or are microorganisms by which much of the population may have been infected. Both on-panel and off-panel organisms tested are shown in Table 5.5.

Samples were prepared by spiking potential cross-reactive organisms into simulated nasopharyngeal swab sample matrix at the highest concentration possible based on the organism stock, preferably 10^5 $TCID_{50}$/mL for viral targets and 10^6 CFU/mL for bacterial and fungal targets. All on-panel samples generated a positive call for every target and all off-panel targets resulted in negative call, with the exception of *B. bronchiseptica* and *B. holmesii* with a cross-reaction with *B. pertussis*. Those cross-reactions were described in the cleared device, and they are expected to not have clinical relevance since the presence of other Bordetella species are usually associated as a co-infection with *Bordetella pertussis*.

Table 5.5: List of Analytical Specificity Pathogens

Pathogen	Cross-reactivity detected
On-Panel	
Bacteria	
Mycoplasma pneumoniae	None
Bordetella pertussis[c]	None
Chlamydophila pneumoniae	None
Viruses	
Influenza A H1N1[c]	None
Influenza A H3N2	None
Influenza A/2009/H1N1	None
Influenza B	None
Human Coronavirus 229E[c]	None
Human Coronavirus OC43[c]	None
Human Coronavirus NL63	None
Human Coronavirus HKU1	None
Parainfluenza virus 1	None
Parainfluenza virus 2	None
Parainfluenza virus 3[c]	None
Parainfluenza virus 4	None
RSV A[c]	None
hMPV[c]	None
Adenovirus A12[c]	None

Pathogen	Cross-reactivity detected
Adenovirus C	None
Adenovirus B	None
Enterovirus D68[c]	None
Rhinovirus[c]	None
Echovirus 6[c]	None
SARS-CoV-2	None
Off-Panel	
Bacteria	
Acinetobacter calcoaceticus	None
Bordetella avium	None
Bordetella bronchiseptica	*Bordetella pertussis*[a]
Bordetella hinzii	None
Bordetella holmesii	*Bordetella pertussis*[a]
Corynebacterium diphteriae[c]	None
Enterobacter aerogenes	None
Haemophilus influenzae[c]	None
Klebsiella oxytoca	None
Lactobacillus acidophilus	None
Legionella feeleii	None
Legionella micdadei	None
Legionella pneumophila[c]	None
Mycobacterium tuberculosis	None
Mycoplasma genitalium	None
Mycoplasma hominis	None[b]
Mycoplasma orale	None
Neisseria elongata	None
Neisseria gonorrhoeae	None
Serratia marcescens	None
Staphylococcus aureus[c]	None
Staphylococcus epidermidis	None
Stenotrophomonas maltophilia /Pseudomonas maltophilia	None
Streptococcus pneumoniae[c]	None
Streptococcus salivarius[c]	None
Ureaplasma urealyticum	None
Escherichia coli (0157)	None
Klebsiella pneumoniae	None
Moraxella catarrhalis /Branhamella catarrhalis	None
Neisseria meningitidis[c]	None
Proteus mirabilis	None
Pseudomonas aeruginosa[c]	None
Staphylococcus epidermidis[c]	None

Pathogen	Cross-reactivity detected
Streptococcus pyogenes	None[b]
Streptococcus agalactiae	None
Viruses	
Bocavirus	None
Cytomegalovirus[c]	None
Epstein-Barr Virus	None
Measles Virus	None
MERS Coronavirus	None
Mumps	None
Severe Acute Respiratory Syndrome (SARS) virus	None
Herpes Simplex Virus 1[c]	None
Herpes Simplex Virus 2	None
Fungi	
Candida albicans[c]	None
Aspergillus flavus	None
Aspergillus fumigatus	None[b]
Cryptococcus neoformans	None

a. As described for the previously cleared device, targeted gene for *Bordetella pertussis* (IS481) is a mobile transposon also present in *B. holmesii* (detected in 6/6 replicates) and some clusters of *B. bronchiseptica* (detected in 3/3 replicates), so observed cross-reaction with *B. pertussis* was expected in both cases.
b. *B. pertussis* was detected with high Ct value (low concentration) for *A. fumigatus* (1/6 replicates), *Mycoplasma hominis* (1/9 replicates) and *S. pyogenes* (2/6 replicates). Proper investigation confirmed *B. pertussis* contamination in all cases. *In silico* analysis confirmed lack of cross-reactivity of *B. pertussis* assay with all three organisms.
c. Pathogen tested in combination with SARS-CoV-2 at 3xLoD resulting in no impact on assay performance.

Since the QIAstat-Dx Respiratory Panel Plus differs only from the previously cleared device (QIAstat-Dx Respiratory Panel) by the addition of primers and probes for SARS-CoV-2 detection and a change in the lysis reagent, *in silico* evaluation of the two SARS-CoV-2 assays was performed to corroborate lack of cross-reactivity of the device. An exclusivity BLAST-based *in silico* screening was performed on week 16, 2022 (April 20th 2022), including all available sequences in GenBank database. No GenBank sequences corresponding to human-infective pathogens were predicted to be positive for the primer/probe sets included in the QIAstat-Dx system to detect SARS-CoV-2.

Interfering Substances

Potential Interfering substances (endogenous, exogenous and technique-specific) were tested at a concentration predicted to be above the levels expected to be found in an authentic NPS specimen for the SARS-CoV-2 target. Interfering substances for all the other targets of the QIAstat-Dx Respiratory Panel Plus have been tested using the cleared device (QIAstat-Dx Respiratory Panel) with the results remaining applicable, as the only

differences between the devices are the addition of SARS-CoV-2 analyte and a change in the lysis reagent .

None of the substances tested showed inhibition of SARS-CoV-2 (see Table 5.6).

Table 5.6: Potential Interfering Substances Concentration without observable inhibitory effect on SARS-CoV-2

Substance Type	Substance / Pathogen	Concentration tested
Endogenous Substances	Human genomic DNA 200 ng/µL	20 ng/µL
	Human Blood (+NaCitrate)	1% v/v
	Mucin from bovine submaxillary glands	1% v/v
Exogenous substances	Tobramycin (systemic antibiotic)	0.6 mg/ml
	Mupirocin	2% w/v
	OCEAN Saline nasal spray	1% v/v
	Afrin®, severe congestion nasal spray (Oxymetazoline HCl)	1% v/v
	Analgesic ointment (Vicks® VapoRub®)	1% w/v
	Petroleum Jelly (Vaseline®)	1% w/v
	Chiroflu Influenza Vaccine (surface antigen inactivated)	0.000001% v/v
Technique Specific Substances	Disinfecting wipes	½ inches2/1 ml UTM
	DNAZap	1% v/v
	ProtectRNA™ RNase Inhibitor 500x Concentrate	1% v/v
	Bleach	5% v/v
	Ethanol	5% v/v
	Swab Copan 168C	1 swab/1 ml UTM
	Swab Copan FloQ	1 swab/1 ml UTM
	Swab Copan 175KS01	1 swab/1 ml UTM
	Swab Puritan 25-801 A 50	1 swab/1 ml UTM
	VTM Sigma Virocult	100%
	VTM Remel® M4-RT	100%
	VTM RT	100%
	BD Universal Viral Transport	100%
	DeltaSwab Virus	100%

Microbial Interference

A microbial interference study was conducted to assess the inhibitory effects of select non-target organisms on the ability to detect SARS-CoV-2. Clinically relevant and challenging concentrations (1.00E+06 CFU/mL for bacteria/fungi, 1.00E+05 PFU/mL for viruses unless otherwise noted) of non-target organisms were individually mixed with SARS-CoV-2 at 3x LoD in simulated NPS matrix. Testing was performed in triplicate with two additional tests performed if SARS-CoV-2 was not detected in one of the original three

replicates. All combinations and replicates successfully detected SARS-CoV-2 except for three samples, one *Legionella pneumophila*, one *Streptococcus salivarius* sample, and one *H.influenzae* sample. For these, additional replicates successfully detected SARS-CoV-2. Where available, at least one additional strain of *L. pneumophila*, *S. salivarius* or *H.influenzae* was also tested in triplicate with all samples successfully detecting SARS-CoV-2. See Table 5.7 for a list of the strains tested and the result summary.

Table 5.7: Microbial Interference Study Results

Non-Target Organism	Strain/Isolate	Source/ Catalog #	# SARS-CoV-2 detected/ valid runs
Staphylococcus aureus[a]	FDA 209	ATCC CRM-6538	3/3
Streptococcus pneumoniae	Z022 19F	ZeptoMetrix 0801439	3/3
Streptococcus salivarius	C699 [S30D]	ATCC 13419	3/3
Streptococcus salivarius	Z127	ZeptoMetrix 0801896	4/5
Haemophilus influenzae	AMC 36-A-7	ATCC 8142	3/3
Haemophilus influenzae	AMC 36-A-1	ATCC 10211	3/3
Candida albicans	CBS 562	ATCC 18804	3/3
Herpes Simplex Virus 1	ATCC-2011-9	ATCC VR-1789	3/3
Staphylococcus epidermidis	Fussel	ATCC 14990	4/5
Pseudomonas aeruginosa	PRD-10	ATCC 15442	3/3
Legionella pneumophila	Philadelphia[b]	ZeptoMetrix 0801645	3/5
Legionella pneumophila	Philadelphia-1[b]	ATCC 33152	3/3
Legionella pneumophila	Los Angeles-1	ATCC 33156	3/3
Neisseria meningitidis[a]	serogroup A	ATCC 13077	3/3
Corynebacterium diphtheriae[a]	48255	ATCC 11913	3/3
Human Cytomegalovirus (CMV)[a]	Towne	Zeptometrix 0810499 CFHI	3/3

[a] *S. aureus* evaluated at $4.5x10^8$ CFU/mL, *N. meningitidis* $1.0x10^3$ CFU/mL, *C. diphtheriae* $1.0x10^3$ CFU/mL, and CMV at $1.0x10^4$ $TCID_{50}$/mL.
[b] Philadelphia and Philadelphia-1 are both designations of strain Philadelphia serogroup-1, differences in naming are due to supplier.

Competitive Inhibition

Clinically relevant co-infections testing demonstrated that when at least two QIAstat-Dx Respiratory Panel Plus pathogens of different concentrations are simultaneously present in one sample all targets can be detected by the assay. SARS-CoV-2 at 3x LoD has been tested in combination with the following on-panel pathogens at high concentrations (10E+05 PFU/mL for viral targets, 10E+06 CFU/mL for bacterial targets), with no impact on assay performance: Coronavirus 229E, Coronavirus OC43, Adenovirus A12, Parainfluenza Virus 3, *Bordetella pertussis*, Enterovirus D68, Echovirus 6, Respiratory Syncytial Virus (RSV), Rhinovirus, hMPV and Influenza A H1N1.

Carryover Study

A carryover study was performed using the QIAstat-Dx Respiratory Panel Plus to evaluate the potential occurrence of cross-contamination between consecutive runs and carryover between cartridge chambers on the QIAstat-Dx Analyzer 1.0. Two panels consisting of high concentrations of influenza A, Parainfluenza virus 3, and *M. pneumoniae* (panel A) or Coronavirus NL63, RSV, and SARS-CoV-2 (panel B) in simulated NPS matrix were each tested multiple times between runs of negative (no analyte) cartridges for a total of 62 runs across several days. No carryover between cartridges or chambers within the cartridges was observed.

Sample Stability

Verification that NPS specimens in Universal Transport Medium (UTM) at the specified conditions does not impact the performance of SARS-CoV-2 when tested with QIAstat-Dx Respiratory Panel Plus compared to freshly tested samples was conducted. A Positive sample (Table 5.8) was prepared in clinical negative matrix spiked with SARS-CoV-2 at 1x and 3x LoD concentration. Negative samples consisted of a clinical negative matrix that were prepared by pooling human negative NPS samples.

Table 5.8: Samples used for Sample Stability Study

Strain information	Source	Catalogue ID	Stock concentration
n/a	Vall d'Hebron hospital – Clinical sample	S1231	1.90E+07 copies/mL

Sample stability testing demonstrated that NPS specimens in Universal Transport Medium (UTM) may be stored at the conditions listed below.

- Room temperature up to 4 hours at 15–25°C
- Refrigerated up to 3 days at approximately 4°C
- Frozen up to 14 days at –20°C

Matrix Equivalency and Single-spiked vs. Multi-spiked Sample Equivalency

A comparison of the performance of analytical SARS-CoV-2 samples prepared in negative clinical NPS matrix to samples prepared in simulated NPS matrix was conducted. In addition, a multi-spiked sample consisting of a subset of original panel analytes was tested together with the SARS-CoV-2 analyte.

The detection limit (1x LoD) for the SARS-CoV-2 pathogen strain defined in clinical NPS matrix as well as one log below the LoD (0.1x LoD) were taken as the reference. Samples were prepared at both concentrations in negative clinical NPS matrix and simulated NPS matrix. 20 replicates were tested for each sample concentration and matrix type using one lot of QIAstat-Dx Respiratory Panel Plus cartridges.

The multi-spiked sample was prepared in simulated matrix at the limit of detection concentration (1x LoD) and one log below (0.1x LoD) from the cleared device (QIAstat-Dx Respiratory Panel, K183597) of each target spiked, along with the SARS-CoV-2 analyte. Twenty replicates were tested for each sample concentration using one lot of QIAstat-Dx Respiratory Panel Plus cartridges.

The matrix equivalency for the SARS-CoV-2 target was confirmed between clinical and simulated NPS matrix. Furthermore, it was confirmed that the performance was not affected when testing the additional analyte (SARS-CoV-2) in a multi-spiked with a subset of original panel analytes.

Precision

Within-laboratory precision was assessed during a study which examined the between-instrument variability at one site by varying test conditions such as cartridge lot, operator and instrument, since the between-site reproducibility has been tested previously with the cleared device (QIAstat-Dx Respiratory Panel, K183597). In addition, only the SARS-CoV-2 target and a subset of original panel analytes were included in the study to bridge the two devices. The testing was performed considering the following variables: across 5 non-consecutive days; two operators; three instruments; total of 90 replicates per sample concentration; sample concentrations of 3x LoD, 1x LoD, and Negative; and three cartridge lots. Analytical combined samples composed of SARS-CoV-2 and a subset of analytes were made by spiking the targets in simulated NPS matrix consisting of UTM and HeLa cells.

Table 5.9 summarizes the results, which met the acceptance criteria.

Table 5.9: Detection rate per analyte and the 2-sided 95% Confidence Interval by target for 1x LoD, 3x LoD and Negative samples

Grouping Variable(s)		Proportion		Two-Sided 95% Confidence Limit	
Pathogen	**Concentration**	**Fraction**	**Percentage**	**Lower**	**Upper**
Flu B	1xLoD	89 / 90	98.89%	93.96%	99.97%
	3xLoD	91 / 92*	98.91%	94.09%	99.97%
	Neg	90 / 90	100.00%	95.98%	100.00%
CorHKU1	1xLoD	90 / 90	100.00%	95.98%	100.00%
	3xLoD	92 / 92*	100.00%	96.07%	100.00%
	Neg	90 / 90	100.00%	95.98%	100.00%
PIV 3	1xLoD	88 / 90	97.78%	92.20%	99.73%
	3xLoD	92 / 92*	100.00%	96.07%	100.00%
	Neg	90 / 90	100.00%	95.98%	100.00%
Rhinovirus	1xLoD	90 / 90	100.00%	95.98%	100.00%
	3xLoD	92 / 92*	100.00%	96.07%	100.00%
	Neg	90 / 90	100.00%	95.98%	100.00%
Adenovirus	1xLoD	87 / 90	96.67%	90.57%	99.31%

Grouping Variable(s)		Proportion		Two-Sided 95% Confidence Limit	
Pathogen	**Concentration**	**Fraction**	**Percentage**	**Lower**	**Upper**
	3xLoD	92 / 92*	100.00%	96.07%	100.00%
	Neg	90 / 90	100.00%	95.98%	100.00%
M. pneumoniae	1xLoD	86 / 90	95.56%	89.01%	98.78%
	3xLoD	90 / 92*	97.83%	92.37%	99.74%
	Neg	90 / 90	100.00%	95.98%	100.00%
SARS-CoV-2	1xLoD	87 / 90	96.67%	90.57%	99.31%
	3xLoD	92 / 92*	100.00%	96.07%	100.00%
	Neg	90 / 90	100.00%	95.98%	100.00%

*Three cartridges showed partial inhibition. Two additional cartridges were run per affected pathogen.

Conclusions

The submitted information in this premarket notification is complete and supports a substantial equivalence determination to the predicate device.