EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
Cue COVID-19 Molecular Test
DECISION SUMMARY

I Background Information:

A De Novo Number

DEN220028

B Applicant

Cue Health Inc.

C Proprietary and Established Names

Cue COVID-19 Molecular Test

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QWB	II	21 CFR 866.3984	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the Cue COVID-19 Molecular Test.

B Measurand:

SARS-Coronavirus 2 (SARS-CoV-2) nucleic acid

C Type of Test:

Isothermal nucleic acid amplification test

III Indications for Use:

A Indication(s) for Use:

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

The Cue COVID-19 Molecular Test is a nucleic acid amplification assay that is used with the Cue Health Monitoring System (Cue Cartridge Reader) for the rapid, qualitative detection of SARS-CoV-2 nucleic acid directly in anterior nasal swab specimens from individuals with signs and symptoms of COVID-19 (i.e., symptomatic).

A negative test result is presumptive, and it is recommended these results be confirmed by a lab-based molecular SARS-CoV-2 assay if necessary for patient management. Negative results do not preclude SARS-CoV-2 infections and should not be used as the sole basis for treatment.

Positive results do not rule out co-infection with other respiratory pathogens.

This test is not a substitute for visits to a healthcare provider or appropriate follow-up and should not be used to determine any treatments without provider supervision.

This test is intended to be sold over-the-counter (OTC) for testing of individuals 18 years of age and older.

B Special Conditions for Use Statement(s):

OTC - Over The Counter

C Special Instrument Requirements:

A mobile smart device with wifi access and the Cue Health Monitoring System (Cue Reader).

IV Device/System Characteristics:

A Device Description:

The device consists of the Cue Health Monitoring System (Cue Reader), the Cue COVID-19 Molecular Test Cartridge, and the Cue sample wand. Users must first download and install the Cue Health App onto their mobile smart device. Users then create an account (first time use) and pair the Cue Reader with the mobile smart device. Multiple profiles can be set up under each user account. The appropriate profile is selected and the user inserts the Cue COVID-19 Molecular Test Cartridge into the Cue Reader. The Cue COVID-19 Molecular Test Cartridge must warm up prior to initiating a run. The user collects an anterior nasal swab sample by swabbing both nares with the Cue sample wand and then inserts the Cue sample wand nasal sample into the port of the Cue COVID-19 Molecular Test Cartridge. The test will start as soon as the Cue Sample Wand is inserted into the Cue COVID-19 Molecular Test Cartridge and is completed in 20 minutes. The Cue Health App will show the Cue COVID-19 Molecular Test result when the test is complete. The result is saved in the Cue Account profile that was selected before the test started.

B Principle of Operation

The Cue COVID-19 Molecular Test Cartridge utilizes isothermal nucleic acid amplification technology for the qualitative detection of SARS-CoV-2 nucleic acids. This test is a molecular nucleic acid amplification test (NAAT) that detects the nucleic acid of SARS-CoV-2 using a molecular amplification reaction. The SARS-CoV-2 target primers amplify a region of the

nucleocapsid (N) gene. The SARS-CoV-2 target forward primer is conjugated to an affinity tag. RNase P serves as the internal control. The RNase P forward primer is conjugated to a different affinity tag. Both SARS-CoV-2 target and RNase P reverse primers are conjugated to an enzyme. Both the SARS-CoV-2 target and RNase P probes bind to the middle-region of the target amplicon. Following target amplification, the amplicons are bound to a functionalized electrode (one for SARS-CoV-2 and one fore RNase P) via the affinity tag conjugated to the forward primer. The enzyme-bound to the reverse primer then catalyzes a redox reaction. The current flow from the electrodes provides a semi-quantitative nanoampere measurement that is converted to a positive or negative result (based on a pre-determined cutoff).

The RNase P internal control has been designed to control for presence of human cellular material in the sample and proper assay execution including sample lysis, inhibition, amplification, and assay reagent function for each critical step. If RNase P is not detected, the Cue COVID-19 Molecular Test will return an "Invalid" result.

When the user inserts the Cue sample wand with anterior nasal sample into the cartridge, the test automatically begins. Heating, mixing, amplification, and detection take place within the cartridge.

C Instrument Description Information

1. Instrument Name:
   Cue Health Monitoring System (Cue Reader).

2. Specimen Identification:
   Anterior Nasal Swabs.

3. Specimen Sampling and Handling:
   Once the sample has been collected, the Cue sample wand is immediately inserted directly into the Cue COVID-19 Molecular Test Cartridge.

4. Calibration:
   Not Applicable.

5. Quality Control:
   Internal Control.

V Standards/Guidance Documents Referenced:

Document Number	Title	Publishing Organization
EP17-A2	Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures, 2nd Edition	CLSI
EP25	Evaluation of Stability of In Vitro Diagnostic Reagents	CLSI
N/A	Content of Premarket Submissions for Software Contained in Medical Devices	FDA

Document Number	Title	Publishing Organization
N/A	Content of Premarket Submissions for Management of Cybersecurity in Medical Devices	FDA
ISO 10993-1:2018	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process	ANSI AAMI ISO
ISO 14971:2019	Medical devices - Applications of risk management to medical devices	ANSI AAMI ISO
IEC 62133:2012	Secondary cells and batteries containing alkaline or other non-acid electrolytes - Safety requirements for portable sealed secondary cells, and for batteries made from them, for use in portable applications	IEC
IEC 60601-1-2:2014	Medical electrical equipment -- Part 1-2: General requirements for basic safety and essential performance -- Collateral Standard: Electromagnetic disturbances -- Requirements and tests	ANSI AAMI IEC

VI Performance Characteristics:

A. Analytical Performance

1. Precision:

A precision study was conducted to assess the total variability of the Cue COVID-19 Molecular Test across testing days, operators, and Cue COVID-19 Molecular Test cartridge lots. The testing panel was with inactivated SARS-CoV-2 (isolate USA-WA1/2020) diluted into clinical nasal matrix and then spiked onto Cue sample wands. The testing panel consisted of four members: (1) Negative (no analyte); (2) $C_{20\text{-}80}$ (0.3xLoD); (3) C_{95} (1xLoD); and (4) C_{100} (2.5xLoD). Cue COVID-19 Molecular Test cartridge lots were tested by two operators each across twelve non-consecutive days, each running two replicates per day (3 lots × 2 operators/lot × 12 days/operator × 2 replicates/day) for a total of 144 observations per panel member. A total of 60 Cue readers were used in this study. The results are presented in Table 1.

Table 1. Result of the Precision for the Cue COVID-19 Molecular Test.

Lot	Operator	Percent agreement with expected results (n/N) (95% Confidence Interval)			
		Negative	$C_{20\text{-}80}$	C_{95}	C_{100}
1	Operator 1	100% (24/24) (86 - 100%)	96% (23/24) (79 - 100%)[a]	92% (22/24) (73 - 99%)	100% (24/24) (86% - 100%)
	Operator 2	96% (23/24) (79 - 100%)[b]	83% (20/24) (63 - 95%)	100% (24/24) (86 - 100%)	100% (24/24) (86% - 100%)
	Overall	98% (47/48) (89% - 100%)	90% (43/48) (77% - 97%)	96% (46/48) (79% - 100%)	100% (48/48) (93% - 100%)
2	Operator 1	96% (23/24) (79 - 100%)	96% (23/24) (79 - 100%)	96% (23/24) (79 - 100%)[c]	100% (24/24) (86% - 100%)
	Operator 2	100% (24/24) (86 - 100%)	92% (22/24) (73 - 99%)	100% (24/24) (86 - 100%)[d]	100% (24/24) (86% - 100%)
	Overall	98% (47/48) (89% - 100%)	94% (44/48) (83% - 99%)	98% (47/48) (89% - 100%)	100% (48/48) (93% - 100%)

Lot	Operator	Percent agreement with expected results (n/N) (95% Confidence Interval)			
		Negative	C_{20-80}	C_{95}	C_{100}
3	Operator 1	100% (24/24) (86 - 100%)	79% (19/24) (58 - 93%)	100% (24/24) (86 - 100%)	100% (24/24) (86% - 100%)
	Operator 2	92% (22/24) (73 - 99%)	92% (22/24) (73 - 99%)	96% (23/24) (79 - 100%)	100% (24/24) (86% - 100%)
	Overall	96% (46/48) (79% - 100%)	85% (41/48) (72% - 94%)	98% (47/48) (89% - 100%)	100% (48/48) (93% - 100%)
Overall		97% (140/144) (93% - 99%)	90% (129/144) (83% - 94%)	97% (140/144) (93% - 99%)	100% (144/144) (97% - 100%)

[a] One cancelled test was repeated.
[b] One invalid result and one cancelled test were repeated.
[c] One invalid result was repeated.
[d] One cancelled test was repeated.

2. Linearity:
This study is not applicable as this test device is a qualitative assay.

3. Analytical Specificity/Interference:
a. *Cross-reactivity*
The cross-reactivity was evaluated by testing various bacteria (23), viruses (22), fungi (3), and pooled nasal wash with the Cue COVID-19 Molecular Test cartridge. Each organism or virus was tested by spiking (b)(4) of the microorganism onto a Cue sample wand. The cross-reactivity was evaluated by the number of SARS-CoV-2 positive results against the expected negative results. The results, presented in Table 2, show that no cross reactivity was observed at the concentrations tested, except for SARS-CoV (coronavirus from 2003 SARS outbreak).

Table 2. Results of Cross-Reactivity Testing for the Cue COVID-19 Molecular Test.

Organism	Concentration	SARS-CoV-2 positive/ replicates tested
Bordetella pertussis	5.95×10^7 CFU/wand	0/3
Chlamydia pneumoniae	7.35×10^5 CFU/wand	0/3
Corynebacterium diphtheriae	2.69×10^7 CFU/wand	0/3
Escherichia coli	5.45×10^6 CFU/wand	0/3[c]
Haemophilus influenzae	3.49×10^6 CFU/wand	0/3
Lactobacillus plantarum	1.57×10^7 CFU/wand	0/3
Legionella pneumophila	9.55×10^7 CFU/wand	0/3[c]
Moraxella/Branhamella catarrhalis	1.64×10^5 CFU/wand	0/3
Mycobacterium tuberculosis	1.15×10^6 CFU/wand	0/3[c]
Mycoplasma pneumoniae	1.35×10^6 CFU/wand	0/3
Neisseria meningitides	3.56×10^6 CCU/wand	0/3

Organism	Concentration	SARS-CoV-2 positive/ replicates tested
Neisseria subflava	1.64×10^7 CFU/wand	0/3
Pseudomonas aeruginosa	8.70×10^6 CFU/wand	0/3
Staphylococcus aureus	4.18×10^7 CFU/wand	0/3
Staphylococcus epidermidis	3.85×10^7 CFU/wand	0/20[b,c]
Streptococcus pneumonia	6.70×10^6 CFU/wand	0/3
Streptococcus salivarius	2.26×10^6 CFU/wand	0/3
Streptococcus pyogenes	9.55×10^6 CFU/wand	0/3
Adenovirus Type 1	1.55×10^6 TCID50/wand	0/20
Adenovirus Type 7	2.29×10^4 TCID50/wand	0/3
Enterovirus Type 70	8.00×10^4 TCID50/wand	0/3
Epstein Barr Virus	3.93×10^5 copies/wand	0/3
Human Coronavirus 229E	1.26×10^3 TCID50/wand	0/3
Human Coronavirus 0C43	5.25×10^3 TCID50/wand	0/3[c]
Human Coronavirus HKU1	9.25×10^5 copies/wand	0/3
Human Coronavirus NL63	5.50×10^3 TCID50/wand	0/3[a]
MERS-Coronavirus (Inactivated)	2.09×10^3 TCID50/wand	0/3
Human Cytomegalovirus	2.09×10^3 TCID50/wand	0/3
Human Metapneumovirus	5.85×10^2 TCID50/wand	0/3
Measles	8.00×10^2 TCID50/wand	0/3
Mumps	4.78×10^4 TCID50/wand	0/3
Parainfluenza 1	6.30×10^3 TCID50/wand	0/3
Parainfluenza 2	2.09×10^3 TCID50/wand	0/3
Parainfluenza 3	4.26×10^5 TCID50/wand	0/3
Parainfluenza 4	2.50×10^4 TCID50/wand	0/3
Rhinovirus type 1A	7.55×10^3 TCID50/wand	0/20
Respiratory Syncytial Virus B	4.78×10^4 TCID50/wand	0/3
Candida albicans	2.51×10^6 CFU/wand	0/3
Influenza Type A	4.80×10^4 TCID50/wand	0/3
Influenza Type B	1.00×10^5 TCID50/wand	0/3
Mycoplasma genitalium	7.19×10^6 copies/wand	0/3
Aspergillus fumigatus	3.40×10^5 CFU/wand	0/3

Organism	Concentration	SARS-CoV-2 positive/ replicates tested
Aspergillus flavus	1.82×10^5 CFU/wand	0/3
Fusobacterium necrophorum	4.33×10^6 CFU/wand	0/3
Bordetella parapertussis (E595)	4.69×10^7 CFU/wand	0/3
Bordetella parapertussis (A747)	3.44×10^7 CFU/wand	0/3
Pooled human nasal wash	(b)(4)	0/3
P.jiroveci-S.cerevisiae Recombinant	(b)(4) CFU/wand	0/3
SARS Coronavirus (SARS-CoV)	10 fold dilution of stock with Ct values from 25-28	1/3

[a] One cancelled test was repeated.
[b] Two cancelled tests were repeated.
[c] One invalid result was repeated.
CCU = color changing units

Additionally, cross-reactivity was assessed by *in silico* analysis of the test primers/probe sequences against the genome sequences of the microorganisms listed in the table above. Except for SARS-CoV (coronavirus from 2003 SARS outbreak), none of the test primer/probe sequences showed (b)(4) to any of the microorganisms analyzed.

b. *Microbial Interference*
Microbial interference was evaluated by testing various bacteria (22), viruses (21), and fungi (3) with the Cue COVID-19 Molecular Test cartridge. Each organism or virus was prepared, at the concentrations listed in Table 3, with inactivated SARS-CoV-2 (isolate USA-WA1/2020) at 3xLoD and then spiked onto Cue sample wands. The results, presented in Table 3, show that no interference was observed at the concentrations tested.

Table 3. Results of Microbial Interference Testing for the Cue COVID-19 Molecular Test.

Organism	Concentration	SARS-CoV-2 positive/ replicates tested
Bordetella pertussis	(b)(4) $\times 10^7$ CFU/wand	3/3
Chlamydia pneumoniae	7.35×10^5 CFU/wand	3/3
Corynebacterium diphtheriae	2.69×10^7 CFU/wand	3/3
Escherichia coli	1.36×10^6 CFU/wand	3/3
Haemophilus influenzae	3.49×10^6 CFU/wand	3/3
Lactobacillus plantarum	1.57×10^7 CFU/wand	3/3
Legionella pneumophila	9.55×10^7 CFU/wand	3/3

Organism	Concentration	SARS-CoV-2 positive/ replicates tested
Moraxella/Branhamella catarrhalis	1.64×10^5 CFU/wand	3/3
Mycobacterium tuberculosis	1.15×10^6 CFU/wand	3/3
Mycoplasma pneumoniae	1.35×10^6 CFU/wand	3/3[a]
Neisseria meningitides	3.56×10^6 CFU/wand	3/3
Neisseria subflava	1.64×10^7 CFU/wand	3/3
Pseudomonas aeruginosa	8.70×10^6 CFU/wand	3/3
Staphylococcus aureus	4.18×10^7 CFU/wand	3/3[a]
Staphylococcus epidermidis	3.85×10^7 CFU/wand	3/3
Streptococcus pneumonia	3.35×10^6 CFU/wand	3/3
Streptococcus salivarius	2.26×10^6 CFU/wand	3/3
Streptococcus pyogenes	9.55×10^6 CFU/wand	3/3
Adenovirus Type 1	1.55×10^6 TCID50/wand	3/3
Adenovirus Type 7	2.29×10^4 TCID50/wand	3/3
Enterovirus Type 70	8.00×10^4 TCID50/wand	3/3[b]
Epstein Barr Virus	3.93×10^5 copies/wand	3/3
Human Coronavirus 229E	7.05×10^2 TCID50/wand	3/3
Human Coronavirus 0C43	5.25×10^3 TCID50/wand	3/3
Human Coronavirus HKU1	9.25×10^5 copies/wand	4/4[a,c]
Human Coronavirus NL63	2.75×10^3 copies/wand	3/3[a]
MERS Coronavirus	2.09×10^3 TCID50/wand	3/3
Human Cytomegalovirus	2.09×10^3 TCID50/wand	3/3
Human Metapneumovirus	5.85×10^2 TCID50/wand	3/3
Measles	8.00×10^2 TCID50/wand	3/3

Organism	Concentration	SARS-CoV-2 positive/ replicates tested
Mumps	4.78×10^4 TCID50/wand	3/3
Parainfluenza 1	6.30×10^3 TCID50/wand	3/3
Parainfluenza 2	2.09×10^3 TCID50/wand	3/3
Parainfluenza 3	2.13×10^5 TCID50/wand	3/3
Parainfluenza 4	2.50×10^4 TCID50/wand	3/3[a]
Rhinovirus type 1A	7.55×10^3 TCID50/wand	3/3
Respiratory Syncytial Virus B	4.78×10^4 TCID50/wand	3/3
Candida albicans	2.51×10^6 CFU/wand	3/3
Influenza Type A	4.80×10^4 TCID50/wand	3/3
Influenza Type B	6.50×10^3 TCID50/wand	3/3
Mycoplasma genitalium	7.19×10^6 copies/wand	3/3
Aspergillus fumigatus	3.40×10^5 CFU/wand	3/3
Aspergillus flavus	1.82×10^5 CFU/wand	3/3
Fusobacterium necrophorum	4.33×10^6 CFU/wand	3/3
Bordetella parapertussis (E595)	4.69×10^7 CFU/wand	3/3
Bordetella parapertussis (A747)	3.44×10^7 CFU/wand	3/3

[a] One cancelled test was repeated.
[b] One invalid result was repeated.
[c] One additional test was run.

b. *Interfering substances.*

An interfering substances study was conducted to assess the performance of the Cue COVID-19 Molecular Test in the presence of medically and/or physiologically relevant concentrations of potentially interfering substances that may be present in anterior nasal swab specimens. Each potentially interfering substance was prepared, at the concentrations listed in Table 4, in negative clinical nasal matrix and in the presence of inactivated SARS-CoV-2 (isolate USA-WA1/2020) at 3xLoD. Samples were spiked onto Cue sample wands. The results, presented in Table 4, show that no interference was observed at the concentrations tested, except for false positive results in the presence of Saline Nasal Spray at 2.0 µL/wand, Chloroseptic lozenge at 2.0 µL/wand, and Rhinallergy 2.0 µL/wand. Limiting statements for these substances have been added to the labeling.

Table 4. Results of Interfering Substances Testing for the Cue COVID-19 Molecular Test.

Substance	Concentration	SARS-CoV-2 positive/ replicates tested	
		Negative Nasal Matrix	3xLoD SARS-CoV-2
Afrin	2.0 µL/wand	0/6	3/3
Saline Nasal Spray	2.0 µL/wand	1/12	3/3
Zicam Allergy Relief	2.0 µL/wand	0/3[a]	3/3
Chloroseptic Max	2.0 µL/wand	0/6	3/3
Neo-Synephrine	2.0 µL/wand	0/6	3/3[a]
Nasacort	0.4 ng/wand	0/6[a]	3/3
Flonase/Fluticasone	0.4 ng/wand	0/6	3/3
Flunisolide	0.4 ng/wand	0/6	3/3
Dexamethasone	5.0 ng/wand	0/6	3/3
Beclomethasone	0.68 ng/wand	0/6	3/3[a]
Mometasone	0.4 ng/wand	0/6[a]	3/3
Budesonide	0.5 ng/wand	0/6	3/3[a]
Chloroseptic Lozenge	2mg/wand	1/12	3/3
Zanamivir (Relenza)	3.0 ng/wand	0/6	3/3
Tamiflu (Oseltamivir phosphate)	0.1ng/wand	0/6	3/3
Xofluza (baloxavir marboixil)	0.1ng/wand	0/6	3/3
Mupirocin	100 ng/wand	0/6	3/3
Tobramycin	25ng/wand	0/6	3/3
Galphimia Glauca	2mg/wand	0/6	3/3
Rhinallergy	2mg/wand	1/12	3/3
Biotin	0.035 ug/wand	0/6	3/3
Mucin	0.5mg/wand	0/3	3/3
Whole Blood	0.5µL/wand	0/3	3/3

[a] One cancelled test was repeated.
N/A = Positive Panel member was not tested at that substance's concentration.

4. Assay Reportable Range:
This section is not applicable as this test device is a qualitative assay.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):
a. *Unopened Kit Stability*
A multi-lot reagent stability study was conducted to establish the shelf-life of the Cue COVID-19 Molecular Test cartridge. Cartridges were stored at temperatures up to 25°C. Three different lots were tested at monthly intervals for up to 9 months. Cartridge stability was evaluated by the agreement with the negative or positive results expected for the testing panel. The testing panel consisted of negative clinical nasal matrix spiked onto Cue sample wands or inactivated SARS-CoV-2 diluted into clinical nasal matrix and then spiked onto

Cue sample wands at 3xLoD. Ten negative and 10 positive Cue sample wands were tested with each lot at each storage duration. All tested negative and positive Cue sample wands produced 100% agreement with the expected results. The study results demonstrated the stability Cue COVID-19 Molecular test cartridge for up to eight months when stored at 22°C.

b. *Shipping Stability*

A reagent stability study was conducted to establish the stability of the Cue COVID-19 Molecular Test cartridge under conditions representing the extreme temperatures and durations anticipated during shipping. Cartridges underwent the summer profile ((b)(4) between 22°C and 40°C) for a total of (b)(4) directly followed by the winter profile ((b)(4) between -10°C and 18°C) for a total of (b)(4). Finally, cartridges were held at controlled temperature and humidity for (b)(4) and then subjected to a series of vibrational and shock simulations. Cartridge stability was evaluated by the agreement with the negative or positive results expected for the testing panel. The testing panel consisted of negative clinical nasal matrix spiked onto Cue sample wands or inactivated SARS-CoV-2 diluted into clinical nasal matrix and then spiked onto Cue sample wands at 3xLoD. (b)(4) negative and (b)(4) positive Cue sample wands were tested with each lot at each storage duration. All tested negative and positive Cue sample wands produced 100% agreement with the expected results. The study results demonstrate the stability of the Cue COVID-19 Molecular test cartridge under anticipated shipping conditions.

6. Detection Limit:

a. *Limit of Detection*

An analytical sensitivity study was conducted to determine the limit of detection (LoD) for the Cue COVID-19 Molecular Test cartridge. The LoD is defined as the lowest concentration (copies per Cue sample wand, copies/wand) at which ≥ 95% of the replicates tested are positive. A preliminary LoD was established by testing four concentrations of inactivated SARS-CoV-2 (isolate USA-WA1/2020) diluted into clinical nasal matrix and spiked onto Cue sample wands. Forty-eight replicates were tested at each dilution by two operators over three days in two lots of the Cue COVID-19 Molecular Test cartridges. The preliminary LoD, established at 20 copies/wand, was confirmed by testing 20 additional replicates with each lot of Cue COVID-19 Molecular Test cartridges at 20 copies/wand and 10 copies/wand. The LoD for the Cue COVID-19 Molecular Test has been established at 20 copies/wand. The results of the LoD study are summarized in the Tables 5 and 6.

Table 5. Results of the Preliminary LoD for the Cue COVID-19 Molecular Test.

Copies/wand	Lot	% Detection (n/N)
(b)(4)	27251K	100% (24/24)
	27140B	100% (24/24)[a]
60	27251K	100% (24/24)
	27140B	91.7% (22/24)[b]
20	27251K	95.8% (23/24)
	27140B	95.8% (23/24)
(b)(4)	27251K	66.7% (16/24)
	27140B	62.5% (15/24)

[a] two cancelled replicates and one invalid replicate were retested.

[b] one cancelled replicate was retested.

Table 6. Results of the Confirmatory LoD for the Cue COVID-19 Molecular Test.

Copies/wand	Lot	Detection
20	27251K	95% (19/20)[a]
	27140B	100% (24/24)[b]
10	27251K	40% (8/20)[c]
	27140B	60% (12/20)

[a] one cancelled replicates and one invalid replicate were retested.
[b] one invalid replicate was retested.
[c] one cancelled replicate was retested.

b. WHO Testing Panel.

The analytical sensitivity was also evaluated using the First WHO International Standard for SARS-CoV-2 RNA. The analytical sensitivity for the Cue COVID-19 Molecular Test is established at 7.7×10^6 IU/mL using the First WHO International Standard for SARS-CoV-2 RNA.

7. Inclusivity

An analytical reactivity study was conducted to evaluate the ability of the Cue COVID-19 Molecular Test to detect multiple SARS-CoV-2 strains that are temporally and geographically diverse. Testing was performed on [redacted] different strains of inactivated virus diluted into clinical nasal matrix and spiked onto Cue sample wands at 3xLoD. The results, presented in Table 7, show that strains were detected at 100% at the target concentrations.

Table 7. Results of Analytical Reactivity Testing for the Cue COVID-19 Molecular Test.

Strain	Concentration (copies/wand)	Percent Detected (n/3)
UK B.1.1.7	60	100% (3/3)[a]
Japan/Brazil P.1	60	100% (3/3)
Japan/Brazil P.1	60	100% (3/3)
South Africa B.1.351	60	100% (3/3)
US NY B1.526	60	100% (3/3)
US NY B1.526	60	100% (3/3)
India B.1.617.1	60	100% (3/3)
India B.1.617.2	60	100% (3/3)
India B.1.617.2	60	100% (3/3)
Italy-INMI1	60	100% (3/3)
Hong Kong/VM20001061/2020	60	100% (3/3)
USA-WA1/2020	60	100% (3/3)
Omicron lineage BA.1	60	100% (3/3)[b]
Omicron lineage BA.1.1	60	100% (3/3)

Strain	Concentration (copies/wand)	Percent Detected (n/3)
Omicron lineage BA.2†	60	100% (3/3)
Omicron lineage BA.5†	60	100% (3/3)

[a] Two cancelled tests were repeated.
[b] One invalid result was repeated.
† genomic RNA was used for this strain instead of inactivated virus.

Additionally, inclusivity was assessed by *in silico* analysis of the test primers/probe sequences against the genome sequences of 353,513 SARS-CoV-2 variants circulating in the United States between March 2022 and November 2022 and deposited in the NCBI and GISAID databases. For strains showing mismatches to the test primers/probe, risk level was then assigned as follows:

- Risk level 1
  - A single mismatch was found in the forward and/or reverse primer alone.
  - A single mismatch was found at the 5' or 3' end of the probe.
  - Up to three deletions in the middle of the probe
- Risk level 2
  - A single mismatch in the middle of the probe.
  - One to two mismatches found anywhere in the probe in addition to one to two mismatches in the forward and/or reverse primer.
  - Up to three deletions in the middle of the probe combined with a single mismatch in the middle of the probe.

Of strains found to be circulating between March 2022 and November 2022, 98.853% had no mismatches, 0.738% of strains were determined to be in risk level 1 and 0.415% of strains were determined to be in risk level 2. Mismatches were further investigated by creating 21 synthetic templates representative of the mismatches found across strains in risk levels 1 and 2. Synthetic templates were spiked onto swabs at various concentrations and tested using the Cue COVID-19 Molecular Test. Fourteen of these were detected at 60 copies/wand and seven were detected at between 200 and 600 copies/wand.

Cue Health continues to perform monthly surveillance of emerging SARS-CoV-2 strains by evaluating the test primers/probe, *in silico*, against sequences deposited in the NCBI and GISAID databases. Updated information on detection of emerging variants of concern can be found at www.cuehealth.com.

8. Assay Cut-Off:
   The assay cutoff was determined in a limit of blank (LoB) study conducted in accordance with CLSI EP17-A2 as the 97th percentile of blank samples results.

9. Accuracy (Instrument):
   Please refer to Section VI.C (Clinical Studies) for the clinical evaluation study and data that establish clinical performance and accuracy of the test device.

10. Carry-Over:

A study was conducted to demonstrate that there is no carryover between samples when using the Cue Reader. In this study, negative clinical matrix samples were processed on the same reader following a high positive sample. In total sixteen samples of alternating negative and positive were run on five Cue Readers each for a total of 40 positive observations and 40 negative observations. All test results were as expected. No evidence of carryover was observed.

B Comparison Studies:

1. Method Comparison:
   Please refer to Section VI.C (Clinical Studies) below for the clinical validation, regarding the method comparison studies.

2. Matrix Comparison:
   Not Applicable.

C Clinical Studies:

A prospective all-comer study enrolled (b)(4) subjects at 13 sites, from December 2020 - February 2021 and November 2021- February 2022 to evaluate the clinical performance of the Cue COVID-19 Molecular Test in symptomatic individuals. Cue system set-up, sample collection, and testing were completed by each subject in a simulated home environment. Each subject was allowed (b)(4) minutes to obtain a Cue COVID-19 Molecular Test result, including a retest if needed due to an initial canceled test or invalid result. A nasal swab sample was then collected by a trained operator for comparator testing. A consensus comparator (agreement between at least two FDA Emergency Use Authorized (EUA) molecular tests for SARS-CoV-2) was used for method comparison.

One subject was excluded due to a protocol deviation; (b)(4) subjects were excluded due to no available Cue result; (b)(4) subjects were excluded due to no available comparator result. There were 902 evaluable subjects with (b)(4) /902) male, (b)(4) /902) female, (b)(4) non-binary, and (b)(4) with unreported gender. The age of participants ranged from 18 years old to 87 years old, with a mean of 40.9 years. The education level of subjects ranged from high school to post-graduate. Results obtained with the Cue COVID-19 Molecular Test were compared to the results obtained with the consensus comparator to determine clinical performance. The results are presented in Table 8.

Table 8. Clinical performance of the Cue COVID-19 Molecular Test.

	EUA authorized RT-PCR Consensus Comparator		Total
	Pos	Neg	
Cue Pos	130	10	140
Cue Neg	10	752	762
Total	140	762	902

- Positive Percent Agreement (PPA) = 92.9% (130/140) (95% CI: 87.4% - 96.1%)
- Negative Percent Agreement (NPA) = 98.7% (752/762) (95% CI: 97.6% - 99.3 %)

1. Clinical Sensitivity:
   Please refer to Section VI.C (Clinical Studies) above for the clinical validation.
   The PPA for the test is 92.9% (130/140) (95% CI: 87.4% - 96.1%)

2. Clinical Specificity:
   Please refer to Section VI.C (Clinical Studies) above for the clinical validation.
   The NPA for the test is 98.7% (752/762) (95% CI: 97.6% - 99.3%)

D Clinical Cut-Off:

There is no clinical cutoff related to the presence of SARS-CoV-2 in patient samples. This section is therefore not applicable.

E Expected Values/Reference Range:

In the Cue COVID-19 Molecular Test clinical study (described in the "Clinical Studies" section above), 246 anterior nasal swab specimens, collected during December 2020 - February 2021 and 656 anterior nasal swab specimens, collected during November 2021- February 2022, were determined to be evaluable. The number and percentage of SARS-CoV-2 positive cases per collection period, as determined by the Cue COVID-19 Molecular Test, are:

- Positivity from December 2020 - February 2021 = (b)(4) (246)
- Positivity from December 2020 - February 2021 = (b)(4) (656)

F Other Supportive Performance Characteristics Data:

1. Usability and User Comprehension

A usability was conducted to assess lay users' execution of Cue Reader set up and Cue COVID-19 Molecular Test workflow. A total of 95 subjects, ages 18 years and older, were enrolled in the study. 98% (93/95) successfully completed testing by receiving a Negative or Positive result for the initial test or upon retest. One subject did not receive a valid Cue test result because no more test cartridges remained for a retest. One subject received a canceled test upon both initial testing and retesting.

Following the usability portion of the study, all subjects were issued a questionnaire. User comprehension was also assessed via a questionnaire completed by 776 subjects enrolled in the clinical study. The questionnaire assessed users' understanding of label comprehension concepts such as the test purpose, interpretation of results, and follow-up actions. The outcome of the study was used to validate the mitigations in the labeling.

2. Frequently Asked Questions

To improve user label comprehension, the labeling includes a Frequently Asked Questions (FAQ) section. The FAQ section was created to provide users information to adequately understand the purpose, limitations, and meaning of the test results as well as where users can access additional information regarding SAR-CoV-2 pathology and epidemiology. The concepts covered in the FAQ section include:

- The purpose of the test and description of the test and the analyte.

- Who should and who should not use the test (self-selection).
- Meaning of the test results.
- When to re-test (e.g., following an invalid result).
- Follow-up for appropriate health management.

3. Hazard Analysis

A comprehensive hazard analysis of the Cue COVID-19 Molecular Test was conducted in accordance with ISO 14971:2019. The hazard analysis included identification of the potential hazard, likelihood of occurrence, severity of potential harm, hazard control measure(s), hazard control verification, and assignment of pre- and post-control risk levels. The elements considered included operator errors (i.e., human factors), sample and device handling and storage, and environmental factors.

Potential sources of errors that could adversely affect system performance were identified and mitigated first through system design and then through additional cautions in the labeling. The identified risks which could result in erroneous test results were evaluated in flex studies that evaluated the functionality of fail-safe mechanisms and stressed the functional limits of the test system (see below)

4. Failsafe Features

The device features a number of failsafe features designed to minimize false results due to user error:

- Internal Control – Monitors for presence of human specimen material; monitors for the execution of each step in the test chemical reaction.
- Internal system timer – Monitors for system timing with respect to cartridge and wand insertion; monitors for correct wand insertion.
- Tilt sensor – Monitors for correct test system positioning.
- Temperature Sensor – Monitors test system temperature; prevents use of cartridges which are not equilibrated to room temperature.
- Cartridge Expiration date sensor – Prevents use of expired cartridges.
- Used Cartridge sensor – Prevents use of used cartridges.
- Battery Charge Sensor – Prevents use of test system when the Cue Reader battery is < 10% charged.

5. Flex Studies

The operational limits of the device were evaluated in a series of experiments simulating conditions of use outside of the intended use environment or in instances of user errors by testing positive (at 3x LoD) and negative samples. Blank samples were Cue sample wands with nothing spiked onto the swab.

The results demonstrated that the test system is robust and that false results can be expected to be reasonably mitigated through the combination fail-safes and labeling.

The following test cases evaluated the effectiveness of the fail-safes on device performance:

Study #	Source of Error	Objective	Description	Results
1a	Improper Wand Insertion	**Fail-safe verification** – verify that a Sample Wand inserted 30 minutes after the test cartridge has been inserted into the Reader and after the cartridge has completed heating will result in a canceled test.	Once the cartridge finished heating a timer was started for 30 minutes. After a minimum of 30 minutes, a blank Sample Wand was inserted.	29/29 tests were cancelled and the appropriate reason was displayed on the Cue Health App screen.
1b	Improper Wand Insertion	**Fail-safe verification** – verify that a Sample Wand inserted prior to the test cartridge completing heating will result in a canceled test.	Immediately after the cartridge was inserted (before preheating was completed), a blank sample wand was inserted into the cartridge.	29/29 tests were cancelled and the appropriate reason was displayed on the Cue Health App screen.
1c	Improper Wand Insertion	**Fail-safe verification** – verify a Sample Wand not fully inserted into the test cartridge shall not initiate a test and will result in a canceled test after 30 minutes.	When prompted by the Cue Health App, a blank sample wand was slowly inserted but not all the way.	29/29 tests were cancelled and the appropriate reason was displayed on the Cue Health App screen.
1d	Improper Wand Insertion	**Fail-safe verification** – verify a Sample Wand inserted into the cartridge prior to the cartridge being inserted in the Reader, will result in a canceled test.	A blank sample wand was inserted into the cartridge, and then the cartridge (with Sample Wand) was inserted into the Reader.	29/29 tests were cancelled and the appropriate reason was displayed on the Cue Health App screen.
1e	Delay in Testing	**Environmental Stress** - assess test performance using samples that are not immediately tested.	Negative and positive samples were incubated at room temperature for five different time durations prior to testing. Samples were then tested according to the user instructions	< 1min hold time • 0/5 negative samples detected. • 5/5 positive samples detected. 5 min hold time • 0/5 negative samples detected. • 5/5 positive samples detected. 10 min hold time • 0/5 negative samples detected. • 4/5 positive samples detected. 15 min hold time • 0/5 negative samples detected. • 5/5 positive samples detected. 30 min hold time • 0/5 negative samples detected. • 5/5 positive samples detected. Overall, there was one false negative result. False results are mitigated by instructions to collect and test samples immediately.

Study #	Source of Error	Objective	Description	Results
2a	Improper Storage Conditions	**Environmental Stress** - assess open pouch stability of cartridges	Test cartridges were unpackaged and incubated at 15°C and 30°C for 30 and 40 minutes each. Each time point and temperature was tested using both negative and positive samples according to the user instructions.	15 °C and 30 min hold time • 0/5 negative samples detected. • 5/5 positive samples detected. 15 °C and 40 min hold time 1/10 negative samples detected. • 5/5 positive samples detected. 30 °C and 30 min hold time • 0/5 negative samples detected. • 5/5 positive samples detected. 30 °C and 40 min hold time • 0/5 negative samples detected. • 9/10 positive samples detected Overall, there was one false negative result and one false positive result. False results are mitigated by instructions to open the cartridge only when ready to test.
2b	Improper Storage Conditions	**Environmental Stress** - assess open pouch stability of cartridges exposed to sunlight for up to the duration of the claimed in-use stability (30 minutes after opening the pouch)	Test cartridges were unpackaged and incubated on a surface that was exposed to sunlight for 10, 20, and 30 minutes. Each time point was tested using both negative and positive samples according to the user instructions.	10 min hold time • 0/20 negative samples detected. Two initial canceled tests were retested. • 20/20 positive samples detected. 20 min hold time • 0/20 negative samples detected. Four initial canceled tests were retested • 20/20 positive samples detected. One initial canceled test was retested. 30 min hold time • 0/20 negative samples detected. • 19/20 positive samples detected. Overall, there was one false negative result. False results are mitigated by instructions to open the cartridge only when ready to test.
2c	Improper Storage Conditions	**Environmental Stress** - assess the stability of cartridges stored frozen, then brought back to room temperature	Test cartridges were stored in final packaging for 72 hours at -20°C. Cartridges were allowed to acclimate to normal temperature for 12 hours. Testing was then performed using both negative and positive samples according to the user instructions.	0/20 negative samples were detected and 19/20 positive samples were detected. Overall, there was one false negative result. False results are mitigated by proper storage conditions in the labeling.
2d	Improper Storage Conditions	**Environmental Stress** - assess the stability of cartridges stored refrigerated, then brought back to room temperature.	Test cartridges were stored in final packaging for 72 hours at 2°C to 8°C and for 72 hours. Cartridges were allowed to acclimate to normal temperature for 12 hours. Testing was performed using both negative and positive samples according to the user instructions.	0/20 negative samples were detected and 20/20 positive samples were detected.

Study #	Source of Error	Objective	Description	Results
2e	Improper Storage Conditions	**Fail-safe verification** – verify that the system recognizes cartridges stored refrigerated and not brought back to room temperature.	Test cartridges were stored in final packaging for 72 hours at 2°C to 8°C and for 72 hours. Cartridges were then inserted into the Reader immediately according to the user instructions.	20/20 tests were cancelled and the appropriate reason was displayed on the Cue Health App screen.
2f	Improper Storage Conditions	**Fail-safe verification** - verify that the system recognizes the cartridges are beyond the Use By Date	Expired cartridges were inserted into the Reader according to the user instructions.	20/20 tests were cancelled and the appropriate reason was displayed on the Cue Health App screen.
2g	Improper Storage Conditions	**Fail-safe verification** - verify that the system recognizes the cartridges have been previously used	Used cartridges were inserted into the Reader according to the user instructions.	20/20 tests were cancelled and the appropriate reason was displayed on the Cue Health App screen.
3	Functionality of the Internal Control	**Fail-safe Verification** -To validate the functionality of the internal control	When prompted by the Cue health App, a blank sample wand was inserted into the cartridge according to the user instructions.	38/40 tests returned an invalid result. Two tests returned a negative result. Failure of the internal control to detect human specimen is mitigated by detailed collection instructions.
4a	Improper Positioning	**Fail-safe verification** – To verify that a test will not start if the Reader is tilted to 20 degrees.	A tilt table was used to position the Cue Reader such that the cartridge port was tilted at 20 degrees in each of four directions (up, down, left, and right). A test cartridge was then inserted into the Reader.	For all 12 inserted cartridges (3 at each of tilt direction), the test was not initiated, and the user was provided with the appropriate tilt warning message to return the Reader to a flat level surface to continue testing.
4 b	Improper Positioning	**Fail-safe verification** – verify that the test will cancel if the Reader is tilted to between 20 and 45 degrees during a test cycle and is not returned to less than 20 degrees within 12 seconds.	When prompted by the Cue Health App, a blank sample wand was inserted into the cartridge according to the user instructions. A tilt table was then used to position the Cue Reader such that the cartridge port was tilted at between 20 and 45 degrees in each of four directions (up, down, left, and right).	For all 12 samples (3 at each of tilt direction), the test was canceled within 12 seconds and the appropriate reason was displayed on the Cue Health App screen.
4c	Improper Positioning	**Fail-safe verification** – verify the test will cancel if the Reader is tilted to greater than 45 degrees during a test cycle.	When prompted by the Cue Health App, a blank sample wand was inserted into the cartridge according to the user instructions. A tilt table was then used to position the Cue Reader such that the cartridge port was tilted at greater than 45 degrees in each of four directions (up, down, left, and right).	For all 12 samples (3 at each of tilt direction), the test was canceled as soon as the reader exceeded 45 degrees and the appropriate reason was displayed on the Cue Health App screen.

Study #	Source of Error	Objective	Description	Results
4d	Improper Positioning	**Environmental Stress** - assess test performance with the reader tilted between 18 and 20 degrees.	A Cue reader was placed on an angled surface such that the cartridge port was tilted at between 18 and 20 degrees in each of four directions (up, down, left, and right). Each tilt direction was tested using both negative and positive samples according to the user instructions.	Up tilt • 0/5 negative samples detected. • 5/5 positive samples detected. Down tilt • 0/5 negative samples detected. • 5/5 positive samples detected. Left tilt • 0/5 negative samples detected. • 5/5 positive samples detected. Right tilt • 0/5 negative samples detected. • 5/5 positive samples detected.
5a	Vibrations	**Environmental Stress** - assess test performance with vibration of the Reader and Cartridge along the x profile.	A Cue Reader was subject to vibrational motion in the horizontal X direction in accordance with IEC 60068 2-64:2000 'Spectrum A2' Vibration (Broadband Random). Then both negative and positive samples were run according to the user instructions. Vibration of the entire system continued throughout testing.	0/58 negative samples were detected. There was one invalid result and one cancelled test. 59/60 positive samples were detected. Overall there was one false negative result. False results are mitigated by warnings not to move the Cue Reader while the test is running.
5b	Vibrations	**Environmental Stress** - assess test performance with vibration of the Reader and Cartridge along the y profile.	A Cue Reader was subject to vibrational motion in the horizontal Y direction in accordance with IEC 60068 2-64:2000 'Spectrum A2' Vibration (Broadband Random). Then both negative and positive samples were run according to the user instructions. Vibration of the entire system continued throughout testing.	2/58 negative samples were detected. There was one invalid result. 59/59 positive samples were detected. There was one cancelled test. Overall there were two false positive results. False results are mitigated by warnings not to move the Cue Reader while the test is running.
5c	Vibrations	**Environmental Stress** - assess test performance with vibration of the Reader and Cartridge along the z profile.	A Cue Reader was subject to vibrational motion in the vertical Z direction in accordance with IEC 60068 2-64:2000 'Spectrum A2' Vibration (Broadband Random). Then both negative and positive samples were run according to the user instructions. Vibration of the entire system continued throughout testing.	1/59 negative samples were detected. There was one cancelled test. 60/60 positive samples were detected. Overall there was one false positive result. False results are mitigated by warnings not to move the Cue Reader while the test is running.

Study #	Source of Error	Objective	Description	Results
6	Atmospheric Pressure	**Environmental Stress -** assess the performance of the Cue Cartridge Reader with the Cue COVID-19 Test Cartridge at "high" altitude.	Positive and negative samples were run according to the user instructions at high altitude (2600m/8530ft).	0/30 negative samples were detected and 30/30 positive samples were detected.
7	Lighting conditions	**Environmental Stress -** verify that the Reader LEDs are visible outdoors.	The Reader was positioned on a table under normal daytime conditions and the viewer was 1 meter away from the Reader. 6 LED light activations on each of 3 Readers were performed.	all 6 LED combinations were accurately called by the 3 viewers from 1 meter away.
8a	Electrical Power	**Fail-safe Verification -** verify that a test will cancel if the Reader is not directly connected to a power supply and runs out of battery charge during test processing.	Readers with a dead batteries were charged to between 1% and 3%. A cartridge was inserted and then prompted by the Cue Health app, a blank sample wand was inserted into the cartridge according to the user instructions. The Reader's battery was depleted before the test completed processing. The Reader was plugged back in to record the result.	3/3 tests were cancelled and the appropriate reason was displayed on the Cue Health App screen.
8b	Electrical Power	**Environmental Stress -** verify the testing process will not be interrupted by power fluctuations via electrical fast transient bursts.	Positive and negative samples were tested according to the user instructions. Readers were subjected to electrical fast transient bursts, in accordance with IEC 61000-4-4, during test processing.	0/3 negative samples were detected. 3/3 positive samples were detected. There was one cancelled test that was re-run.
8c	Electrical Power	**Environmental Stress -** verify the testing process will not be interrupted by power fluctuations via electrical surges.	Positive and negative samples were tested according to the user instructions. Readers were subjected to power fluctuations via electrical surges, in accordance with IEC 61000-4-4, during test processing.	0/3 negative samples were detected. 3/3 positive samples were detected.
8d	Electrical Power	**Environmental Stress -** verify that the testing process will not be interrupted by power fluctuations via electrical voltage dips/interruptions.	Positive and negative samples were tested according to the user instructions. Readers were subjected to electrical voltage dips/interruptions, in accordance with IEC 61000-4-4, during test processing.	0/3 negative samples were detected. 3/3 positive samples were detected.

Study #	Source of Error	Objective	Description	Results
8e	Electrical Power	**Fail-safe Verification** - verify a test will not start if the Reader is below 10% battery level.	Using Readers with battery level less than 10%, a test cartridge was inserted into the Reader.	For all three cartridges, the test did not start, and the Cue Health App provided a Reader Battery Low warning, with instructions to connect the Reader directly to a power source to continue with the testing process.
8f	Electrical Power	**Environmental Stress** - verify that testing can be completed with the Reader at a 10% battery level.	Using Readers with battery level at 10%, a test cartridge was inserted into the Reader. Both positive and negative samples were run according to the user instructions.	0/3 negative samples were detected. 3/3 positive samples were detected.
9	Dropping	**Environmental Stress** - assess test performance after dropping the test cartridge and Reader.	Ten cartridges and five Readers were both dropped from a height of three feet. Both positive and negative samples were run according to the user instructions using the dropped items.	Dropped Cartridges • 0/5 negative samples detected. • 5/5 positive samples detected. Dropped Readers • 0/5 negative samples detected. • 5/5 positive samples detected.

VII Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

VIII Identified Risks and Mitigations:

Identified Risks to Health	Mitigation Measures
False Results	Certain labeling information including limitations, device descriptions, performance information, and explanations of procedures as identified in special controls (1), (2), (3), (4), (5). Certain design verification and validation including documentation of device descriptions, certain analytical studies and clinical studies, risk analysis strategies identified in special control (6). Testing of characterized viral samples and labeling information identified in special control (7).
Failure to correctly interpret test results	Certain labeling information including limitations, device descriptions, performance information, and explanations of procedures as identified in special controls (1), (2), (3), (4), (5). Certain design verification and validation including documentation of device descriptions, certain analytical studies and

Identified Risks to Health	Mitigation Measures
	clinical studies, risk analysis strategies identified in special control (6).
Failure to correctly operate the device	Certain labeling information including limitations, device descriptions, performance information, and explanations of procedures as identified in special controls (1), (2), (3), (4), and (5). Certain design verification and validation including documentation of device descriptions, certain analytical studies and clinical studies, risk analysis strategies identified in special control (6).

IX Benefit/Risk Assessment:

A Summary of the Assessment of Benefit:

The probable benefits of this device were found to include facilitating easy-to-use detection of COVID-19 in a home environment, with the potential to test an entire household using a single test reader with multiple cartridges. The unmet need met by this test is to allow for at-home performance of a rapid molecular IVD for SARS-CoV-2. Molecular tests are generally more sensitive and specific compared to the now widely available rapid antigen tests and have been considered the standard of care in guiding the isolation and treatment of patients with both symptomatic and asymptomatic COVID-19 in health care settings. Home-based testing for COVID-19 has several important advantages as detailed above, including decreasing time and effort requirements, shortening the time to diagnosis and therefore treatment, reducing infectious exposures during the process, and lessening demand on overburdened public health and clinical labs during times of increased transmission. For persons facing particular barriers to accessing care outside the home, whether due to physical factors (e.g., vision or mobility impairment), cognitive factors (e.g., learning disability or dementia), or demographic factors (e.g., low income, limited health literacy, geographic distance to medical facilities), at-home OTC tests may potentially help improve equity in early diagnosis, treatment, and improved outcomes of COVID-19.

B Summary of the Assessment of Risk:

The risks associated with the device, when used as intended, are those related to the risk of false or invalid test results, failure to correctly interpret the test results, and failure to correctly operate the device. False positive SARS-CoV-2 results may lead to unnecessary treatment for SARS-CoV-2 with antiviral medication, unnecessary isolation, and delayed diagnosis and treatment of other infections or health conditions. False negative SARS-CoV-2 results may lead to missing and not appropriately treating or monitoring a patient who has SARS-CoV-2 infection. False negative SARS-CoV-2 results may also lead to unnecessary additional diagnostic evaluation or treatment and delay in correct diagnosis or further spread of disease, which may lead to novel cases of infection and concomitant increase in patient morbidity and mortality. Invalid test results may lead to unnecessary delays while additional testing is sought, possibly leading to missed opportunity to initiate time-sensitive treatment, and/or to infecting additional persons.

Compared to tests obtained in person with a HCP, OTC tests performed in the home environment carry the following additional risks: inadequate sample collection (resulting in an inadequate or contaminated sample), incorrect operation of the device (resulting in incorrect or invalid test results), and misinterpretation of test results by the lay user (resulting in incorrect diagnosis and/or actions, resulting in additional preventable harm to the health of the user or others).

C **Summary of the Assessment of Benefit-Risk:**

The device's performance observed in the clinical study suggests that errors will be uncommon and are mitigated by the device on-screen Labeling. The greatest magnitude of risk is that of inaccurate (mainly false negative, leading to a missed or delayed diagnosis of COVID-19, accompanied by the negative medical and epidemiologic consequences detailed above) test results combined with the absence of medical supervision, result interpretation, and care of a person with risk factors for severe disease. This risk is mitigated by providing repeated and clear guidance in the Labeling and IFU for the user to contact an HCP if evidence of worsening disease or risk factors for severe disease are present. With the addition of the special controls the benefits of this device to the intended use population and in the intended use settings presently outweigh the risks.

X **Conclusion:**

The De Novo request is granted, and the device is classified under the following and subject to the special controls identified in the letter granting the De Novo request:

Product Code(s): QWB
Device Type: Over-the-counter molecular test to detect SARS-CoV-2
Class: II
Regulation: 21 CFR 866.3984