

SPECIAL 510(k): Device Modification Decision Summary

To: Center for Disease Control and Prevention (CDC) **RE:** k123905

This 510(k) submission contains information/data on modifications made to the SUBMITTER'S own Class II or Class I device requiring 510(k). The following items are present and acceptable

1. The name and 510(k) number of the SUBMITTER'S previously cleared device:

Trade Name: CDC Human Influenza Virus Real-time RT-PCR Diagnostic Panel

510(k) number: k111507 (also k080570 and k101564)
2. Submitter's statement that the **INDICATION/INTENDED USE** of the modified device as described in its labeling **HAS NOT CHANGED** along with the proposed labeling which includes instructions for use.
3. A description of the device **MODIFICATION(S)**. The modification presented in this 510(k) is the modification of the package insert of the device so that the results for a specimen that tests positive for InfA, H3, and pdmInfA markers and negative for H1 and pdmH1 markers will be interpreted as a presumptive positive for H3N2v influenza A virus detection.

The submitter provided the following LoD, Analytical Reactivity, and Clinical Specimen Testing data:

Limit of Detection (LoD)

The LoD of the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel for influenza A(H3N2) variant ((H3N2)v) virus was evaluated with two recent isolates by determining the lowest concentration of virus as measured by 50% egg infectious dose (EID₅₀/ml) where the InfA, pdmInfA, and H3 primer and probe sets demonstrated a uniform detection rate of ≥ 95%. The results are summarized in the table below.

(H3N2)v LoD Summary

Influenza A(H3N2)v virus	Limit of Detection (EID ₅₀ /mL)			
	InfA	pdm InfA	H3	Final LoD
A/West Virginia/06/2011	10 ^{0.7}	10 ^{1.4}	10 ^{2.1}	10 ^{2.1}
A/Indiana/12/2012	10 ^{0.6}	10 ^{1.3}	10 ^{2.0}	10 ^{2.0}

Analytical Reactivity/Inclusivity

Recent isolates of influenza A (H3N2)v virus from 2009 - 2012 were evaluated with the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel at virus concentrations of approximately 10^{2.0} EID₅₀/ml. The inclusivity testing verifies that the device can detect contemporary influenza A (H3N2)v viruses near the LoD. The results are summarized in the following table.

Inclusivity Testing

Strain designation	EID ₅₀ /mL	Average InfA Ct Value (n=3)	Average pdm InfA Ct Value (n=3)	Average H3 Ct Value (n=3)
A/Kansas/13/2009	10 ^{2.0}	33.4	32.6	33.9
A/Indiana/08/2011	10 ^{2.3}	33.0	33.5	35.6
A/Wisconsin/12/2011	10 ^{2.1}	28.9	26.9	28.9
A/West Virginia/06/2011	10 ^{2.9}	28.1	28.3	30.1
A/Indiana/12/2012	10 ^{2.1}	31.7	32.8	36.0

Clinical Specimen Testing

From July 2012 to August 2012, a total of 165 human respiratory specimens that tested positive for InfA, H3, and pdmInfA markers and negative for H1 and pdmH1 markers with the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel were transferred from U.S. public health laboratories to the CDC for confirmatory testing.

The specimens were retested upon arrival with the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel following the instructions for use provided in the package insert. Results were confirmed through genetic sequence analysis. Comparison of the results obtained with the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel to the results of the genetic sequencing analysis demonstrated a positive percent agreement of 97.6% with a 95% confidence interval of 93.9-99.1 % for the detection of influenza A (H3N2)v virus.

Clinical Performance Comparison

	Comparator ¹		Performance
	Positive ²	Negative	
CDC Flu rRT-PCR Dx Panel (+)	161	NA	97.6% Positive Percent Agreement (93.9 – 99.1) 95% CI
CDC Flu rRT-PCR Dx Panel (-)	4	NA	NA
Total	165	NA	NA

¹The comparator is genetic sequence analysis.

²A positive result for InfA, H3, and pdmInfA markers (negative for H1 and pdmH1 markers) was investigated. Any result that was not positive for all three markers InfA, pdm InfA, and H3 was considered as negative.

NA = not applicable.

- The **FUNDAMENTAL SCIENTIFIC TECHNOLOGY** of the modified device **has not changed**.
- Comparison Information** (similarities and differences) to applicant's legally marketed predicate device including, labeling, intended use, and physical characteristics:

Similarities

	CDC Human Influenza Virus Real-time PCR Diagnostic Panel (k111507)	Modified CDC Human Influenza Virus Real-time PCR Diagnostic Panel (k123905)
Intended Use	<p>The CDC Human Influenza Virus Real-Time PCR Diagnostic Panel is intended for use in Real-time RT- PCR assays on an Applied Biosystems (ABI) 7500 Fast Dx Real-Time PCR Instrument in conjunction with clinical and epidemiological information:</p> <ul style="list-style-type: none"> • For qualitative detection of influenza virus type A or B from viral RNA in upper respiratory tract clinical specimens (including nasopharyngeal swabs, nasal swabs, throat swabs, nasal aspirates, nasal washes and dual nasopharyngeal/throat swabs), and lower respiratory tract specimens (including bronchioalveolar lavages, bronchial washes, tracheal aspirates, sputum, and lung tissue) from human patients with signs and symptoms of respiratory infection and/or from viral culture • For determination of the subtype of seasonal human influenza A virus as seasonal A/H1, A/H3, and/or A/H1pdm09 from viral RNA in upper respiratory tract clinical specimens (including nasopharyngeal swabs, nasal swabs, throat swabs, nasal aspirates, nasal washes and dual nasopharyngeal/throat swabs), and lower respiratory tract specimens (including bronchioalveolar lavages, bronchial washes, tracheal aspirates, sputum, and lung tissue) from human patients with signs and symptoms of respiratory infection and/or from viral culture • For the presumptive identification of virus in patients who may be infected with influenza A subtype A/H5(Asian Lineage) from viral RNA in human respiratory specimens and viral culture in conjunction with clinical and epidemiological risk factors • To provide epidemiologic information for surveillance of the circulating influenza viruses. <p>Performance characteristics for influenza were established during a season when influenza viruses A/H1 and A/H3 were the predominant influenza A viruses in circulation and during a season when the A/H1pdm09 influenza virus was the predominant influenza A virus in circulation. Performance characteristics may vary with other emerging influenza A viruses.</p> <p>Testing with the influenza H5a and H5b primer and</p>	Same

	<p>probe sets should not be performed unless the patient meets the most current U.S. Department of Health and Human Services (DHHS) clinical and epidemiologic criteria for testing suspect A/H5 specimens. The definitive identification of influenza A/H5 (Asian lineage) either directly from patient specimens or from virus cultures requires additional laboratory testing, along with clinical and epidemiological assessment in consultation with national influenza surveillance experts.</p> <p>Negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other patient management decisions. Conversely, positive results do not rule out bacterial infection or co-infection with other viruses. The agent detected may not be the definite cause of disease.</p> <p>If infection with a novel influenza A virus is suspected based on current clinical and epidemiological screening criteria recommended by public health authorities, specimens should be collected with appropriate infection control precautions for novel virulent influenza viruses and sent to state or local health department for testing. Viral culture should not be attempted in these cases unless a BSL 3+ facility is available to receive and culture specimens.</p> <p>All users, analysts, and any person reporting results from use of this device should be trained to perform and interpret the results from this procedure by a competent instructor prior to use. CDC Influenza Division will limit the distribution of this device to only those users who have successfully completed a training course provided by CDC instructors or designees.</p>	
Technology	Real-time RT-PCR	Same
Organism Detected	Universal influenza A viruses (animal and human), Swine-origin influenza A viruses, Influenza B viruses, and Influenza A subtypes: seasonal A/H1, A/H3, A/H1pdm09, and A/H5	Same
Required Instrumentation	Applied Biosystems 7500 Fast Dx Real- Time PCR Instrument	Same
Nucleic Acid Extraction	Yes	Same
Extraction Method	<ul style="list-style-type: none"> • QIAamp[®] Viral RNA Mini Kit, Qiagen Inc. • MagNA Pure Compact -Total Nucleic Acid Kit, Roche Applied Science • MagNA Pure Compact – RNA Isolation Kit, Roche Applied Science • MagNA Pure LC - RNA Isolation Kit II, Roche Applied Science • Qiagen QIAcube with QIAamp[®] Viral RNA Mini Kit, Qiagen Inc. • NucliSENS[®] easyMAG[®], bioMerieux 	Same
Enzyme Master Mix	Invitrogen SuperScript [™] III Platinum [®] One-Step Quantitative RT-PCR Kits (with or without ROX)	Same

Differences

	CDC Human Influenza Virus Real-time PCR Diagnostic Panel (k111507)	Modified CDC Human Influenza Virus Real-time PCR Diagnostic Panel (k123905)
Non Standard Results Interpretation Guidance in the Package Insert	Results positive for InfA, H3, and pdmInfA markers and negative for H1 and pdmH1 markers are reported as inconclusive and referred to CDC for further testing.	Results positive for InfA, H3, and pdmInfA markers and negative for H1 and pdmH1 markers are interpreted as a presumptive positive for influenza A (H3N2) variant virus and referred to CDC for further testing.

6. Design Control Activities Summary:

a) Risk Analysis:

A risk analysis for the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel was conducted and the results reviewed to verify that the change did not present increased or new risks to the user. No new risks were identified as a result of the proposed modification. As an additional mitigation, (H3N2)v influenza strains will continue to be referred to CDC for further confirmation.

The following table is a summary of the risk analysis:

Device Modification	Cause of Risk	Hazardous Situation	Consequence	Risk Control Measure	Risk Acceptability Criteria	Verification Method	Summary Conclusion
<p>Change in results interpretation will allow public health labs to report presumptive positives for the (H3N2)v virus.</p>	<p>Current device results interpretation guidance does not allow for the conclusive identification and reporting of H3N2v virus</p>	<p>(H3N2)v may be present in human respiratory specimens but not conclusively identified by the device.</p>	<p>Patient or community with (H3N2)v infections may not be identified in a timely fashion, leading to a delay in implementation of public health mitigation measures</p>	<p>A combination of measures are used to control risk:</p> <ul style="list-style-type: none"> -Characterization of the performance of the device with (H3N2)v viruses. -Provide users with additional guidance on the results interpretation of the device -Provide users with instructions on reporting results and referral of specimens with presumptive positive results for (H3N2)v to CDC for confirmation -Non-standard results are reported to CDC and referred for further analysis 	<p>Only trained laboratories are allowed to order the device.</p> <p>Analytical and clinical sensitivity of the device for (H3N2)v must be comparable with the detection of human seasonal influenza A viruses.</p> <p>Device labeling must be updated to include results interpretation guidance and instructions on referral of specimens with presumptive positive results for(H3N2)v to CDC for confirmation</p>	<p>Internal controls allow only trained public health laboratories to order the device.</p> <p>LoD, inclusivity, and clinical testing done in accordance with the test methods cleared in the predicate. (k111507)</p> <p>Updated device instructions for use.</p>	<p>Test results demonstrate that the risk of a delay in the identification of (H3N2)v viruses is mitigated to as low as reasonably possible (ALARP).</p> <p>Based on the results of the analytical and clinical testing, the device is capable of sensitive detection of (H3N2)v viruses.</p>

	Incorrect Diagnosis	Specimen is negative for (H3N2)v but device reports positive	Incorrect reporting of patient results; unnecessary public health investigation and expenditure of resources.	<p>A combination of measures are used to control risk:</p> <ul style="list-style-type: none"> -Only trained users are allowed to receive the device -Specificity of the device is demonstrated. -Specimens with presumptive positive results for(H3N2)v or other non-standard results are referred to CDC for further analysis 	<p>Only trained public health laboratories are allowed to order the device</p> <p>The device must have high level of analytical and clinical specificity.</p>	<p>Internal controls allow only trained public health laboratories to order the device.</p> <p>High levels of specificity were previously demonstrated in the cleared predicate.</p>	<p>Test results demonstrate that the risk of an incorrect diagnosis of a specimen as presumptively positive for (H3N2)v have been mitigated to as low as reasonably possibly (ALARP).</p>
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b) LoD, Analytical Reactivity/Inclusivity testing, and testing of clinical specimens were conducted as described in section 3, Device Modifications.

c) Declaration of Conformity

A “Declaration of Conformity” statement was submitted for the manufacturing facility and verification activities and signed by the Deputy Branch Chief, Division of the Scientific Resources, CDC, and the Acting Branch Chief, Virus Surveillance and Diagnostic Branch, CDC, respectively. The statements indicate that:

1. The manufacturing facility is in conformance with design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review.
2. The verification activities, as required by the risk analysis, for the modification were performed by the designated individuals and the results demonstrated that the predetermined acceptance criteria were met.

In conclusion, based on both the results of the analytical testing, clinical specimens testing, and the risk management report, the modified labeling is truthful and accurate. The changes do not affect the performance of the test and it is therefore substantially equivalent to the current cleared test.

7. A Truthful and Accurate Statement, a 510(k) Summary, and the Indications for Use Enclosure.

The labeling for this modified subject device has been reviewed to verify that the indication/intended use for the device is unaffected by the modification. In addition, the submitter’s description of the particular modification and the comparative information between the modified and unmodified devices demonstrate that the fundamental scientific technology has not changed. The submitter has provided the design control information as specified in The New 510(k) Paradigm. On this basis, I recommend the device be determined substantially equivalent to the previously cleared device.