510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K243274

B Applicant

Centers for Disease Control and Prevention

C Proprietary and Established Names

CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel: Influenza A/B Typing Kit (VER 2), Influenza A Subtyping Kit (VER 4), Influenza B Lineage Genotyping Kit (VER 1.1 and 2), and Influenza A/H5 Subtyping Kit (VER 4)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
OZE	Class II	21 CFR 866.3980 - Respiratory Viral Panel Multiplex Nucleic Acid Assay	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To establish a Predetermined Change Control Plan (PCCP) to validate certain future device modifications for the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel, Influenza A/B Typing Kit (VER 2), Influenza A Subtyping Kit (VER 4), Influenza B Lineage Genotyping Kit (VER 1.1 and 2), and Influenza A/H5 Subtyping Kit (VER 4).

B Measurand:

Influenza A, influenza B, seasonal human influenza A(H3), seasonal human influenza A(H1)pdm09, B/Victoria genetic lineage of human influenza B, B/Yamagata genetic lineage of human influenza B, and influenza A subtype A(H5) (Asian lineage) viral RNA target sequences.

C Type of Test:

Real-time RT-PCR (rRT-PCR) assays.

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel, Influenza A/B Typing Kit (VER 2):

The Influenza A/B Typing Kit contains reagents and controls of the Centers for Disease Control and Prevention (CDC) Human Influenza Virus Real-Time reverse transcription time RT-PCR (rRT-PCR) assays on an in vitro diagnostic real-time PCR instrument that has been U.S Food and Drug Administration (FDA)-cleared for use with this kit in conjunction with clinical and epidemiological information:

• For qualitative detection of influenza virus type A or B viral ribonucleic acid (RNA) in upper respiratory tract clinical specimens (including nasopharyngeal swabs [NPS], nasal swabs [NS], throat swabs [TS], nasal aspirates [NA], nasal washes [NW] and dual nasopharyngeal/throat swabs [NPS/TS]) and lower respiratory tract specimens (including bronchoalveolar lavage [BAL], bronchial wash [BW], tracheal aspirate [TA], sputum, and lung tissue) from human patients with signs and symptoms of respiratory infection and/or from viral culture.

• To provide epidemiologic information for surveillance of circulating influenza viruses.

Performance characteristics for influenza were established during a season when seasonal influenza viruses A(H1N1) and A(H3N2) were the predominant influenza A viruses in circulation and during a season when the A(H1N1)pdm09 influenza virus was the predominant influenza A virus in circulation. Performance characteristics may vary with other emerging influenza A viruses.

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.

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.

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.

CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel, Influenza A Subtyping Kit (VER 4):

The Influenza A Subtyping Kit contains reagents and controls of the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel and is intended for use in real-time RT-PCR (rRT-PCR) assays on an in vitro diagnostic real-time PCR instrument that has been FDA-cleared for use with this kit in conjunction with clinical and epidemiological information:

• For determination of the subtype of seasonal human influenza A viruses as seasonal A(H3) and/or A(H1)pdm09 from viral RNA in upper respiratory tract clinical specimens (including nasopharyngeal swabs [NPS], nasal swabs [NS], throat swabs [TS], nasal aspirates [NA], nasal washes [NW], and dual nasopharyngeal/throat swabs [NPS/TS]) and lower respiratory tract specimens (including bronchoalveolar lavage [BAL], bronchial wash [BW], tracheal aspirate [TA], sputum, and lung tissue) from human patients with signs and symptoms of respiratory infection and/or from viral culture;

• To provide epidemiologic information for surveillance of circulating influenza viruses.

Performance characteristics for influenza were established during a season when seasonal influenza viruses A(H1N1) and A(H3N2) were the predominant influenza A virus in circulation. Performance characteristics may vary with other emerging influenza A viruses.

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.

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 influenza viruses and sent to state or local health department for testing. Viral culture should not be attempted unless a BSL 3E facility is available to receive and culture specimens.

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.

CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel, Influenza B Lineage Genotyping Kit (VER 1.1 and VER 2):

The Influenza B Lineage Genotyping Kit contains reagents and controls of the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel and is intended for use in real-time RT-PCR (rRT-PCR) assays on an in vitro diagnostic real-time PCR instrument that has been FDA-cleared for use with this kit in conjunction with clinical and epidemiological information:

• For the determination of the genetic lineage of human influenza B viruses as B/Victoria or B/Yamagata lineage from viral RNA in upper respiratory tract clinical specimens (including nasopharyngeal swabs [NPS], nasal swabs [NS], throat swabs [TS], nasal aspirates [NA], nasal

washes [NW] and dual nasopharyngeal/throat swabs [NPS/TS]) from human patients with signs and symptoms of respiratory infection and/or from viral culture;

• To provide epidemiologic information for surveillance of circulating influenza viruses.

Performance characteristics for influenza B lineage genotyping were established during a season when influenza B/Victoria and B/Yamagata lineages were in circulation.

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.

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.

CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel, Influenza A/H5 Subtyping Kit (VER 4):

The Influenza A/H5 Subtyping Kit contains reagents and controls of the Centers for Disease Control and Prevention (CDC) Human Influenza Virus Real-Time RT-PCR Diagnostic Panel and is intended for use in real-time RT-PCR (rRT-PCR) assays on an in vitro diagnostic real-time PCR instrument that has been FDA-cleared for use with this kit in conjunction with clinical and epidemiological information:

• 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, conjunctival swabs, and viral culture in conjunction with clinical and epidemiological risk factors;

• To provide epidemiologic information for surveillance of circulating influenza viruses.

Performance characteristics for influenza were established during a season when seasonal influenza viruses A(H1N1) and A(H3N2) were the predominant influenza A viruses in circulation and during a season when the A(H1N1)pdm09 influenza virus was the predominant influenza A virus in circulation. Performance characteristics may vary with other emerging influenza A viruses.

Testing with the influenza H5a and H5b primer and 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.

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.

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 unless a BSL 3E facility is available to receive and culture specimens.

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.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only
For *in vitro* diagnostic Use Only

D Special Instrument Requirements:
Not Applicable

IV Device/System Characteristics:

A Device Description:
No changes were made to the device description under the PCCP. Refer to K243931 for device description.

This device includes a PCCP for modifications to the FDA-cleared CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel VER 01. See Section V.C. for the changes included in the PCCP.

B Principle of Operation:
No changes were made to the principle of operations under the PCCP. Refer to K243931 for description of test operation.

V Substantial Equivalence Information:

A Predicate Device Name(s):
CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel, Influenza A/B Typing Kit (VER 2), Influenza A Subtyping Kit (VER 4), Influenza B Lineage Genotyping Kit (VER 1.1. and 2), and Influenza A/H5 Subtyping Kit (VER 4).

B Predicate 510(k) Number(s):
K243931

C Comparison with Predicate(s):
The subject device is similar to the predicate (K243931), having the same intended use, and the same technological characteristics, with the exception of implementation of a PCCP for modifications to the FDA-cleared CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel VER 01 that specifies the validation protocols and acceptance criteria for evaluating the following modifications:

1. Addition of a real-time PCR instrument that is IVD-labeled and used in accordance with its instructions for use.
2. Addition of PCR master mix that is IVD-labeled and used in accordance with its instructions for use or assessed and determined to be acceptable by the CDC's lot-by-lot quality assurance program.
3. Addition of:
    a) A manual extraction method that is IVD-labeled and used in accordance with its instructions for use.
    b) Nucleic acid extraction reagents that are IVD-labeled and used in accordance with their instructions for use as part of a cleared manual extraction procedure.
    c) An automated extraction instrument that is IVD-labeled and used in accordance with its instructions for use.
    d) Nucleic acid extraction reagents that are IVD-labeled and used in accordance with their instructions for use with a cleared automated extraction instrument.
4. Modification of the quencher on the oligonucleotide probes that are manufactured under good manufacturing practices (GMP).

VI Validation Studies and Acceptance Criteria to Support PCCP Modifications

Specific test methods for clinical and analytical validation are specified in the PCCP for modifications to the FDA-cleared CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel VER 01. The following validation studies will be performed in accordance with the PCCP depending on the device modification:

1. Clinical evaluation designed according to established and FDA accepted approaches, with established acceptance criteria FDA found appropriate during this review, to demonstrate substantial equivalence to the predicate device. Clinical performance studies will be conducted to evaluate the following changes according to the established PCCP: addition of a real-time PCR instrument, addition of an automated extraction instrument, addition of nucleic acid extraction reagents or manual extraction method, addition of PCR master mix, or modification of the quencher on the oligonucleotide probes.
2. Limit of Detection (LoD) evaluation with live or inactivated virus according to established and FDA accepted approaches, with established acceptance criteria that FDA found appropriate during this review, to demonstrate substantial equivalence to the predicate device. An LoD study will be conducted, according to the established PCCP, to evaluate the addition of a real-time PCR instrument, addition of an automated extraction instrument, addition of nucleic acid extraction reagents or manual extraction method, addition of PCR master mix, or modification of the quencher on the oligonucleotide probes.
3. Reproducibility study that is designed according to established and FDA accepted approaches, with established acceptance criteria FDA found appropriate during this review, to demonstrate substantial equivalence to the predicate device. A reproducibility study will be conducted, according to the established PCCP, to evaluate addition of a real-time PCR instrument or addition of an automated extraction instrument.
4. Carry-over study demonstrating agreement with expected results compared to the predicate device. A carry-over study will be conducted, according to the established PCCP, to evaluate addition of a real-time PCR instrument or addition of an automated extraction instrument.

This PCCP will enable CDC to address evolving public health needs more quickly by making device changes without premarket review. This will help prevent an interruption in testing capability when there is a discontinuation or supply issue for certain instruments and reagents.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   Precision/reproducibility data for the CDC Human Influenza Real-Time RT-PCR Diagnostic Panel were reviewed and previously found acceptable in K200370, K190302, K172091, K153148, K141859, K130551, K111507, and K080570. A reproducibility study will be conducted to evaluate addition of a real-time PCR or addition of an automated extraction instrument, according to the established PCCP. Data demonstrating pre-specified agreement with the expected results will be considered acceptable to support these modifications to the device.

2. Linearity:
   Not Applicable. This is a qualitative test.

3. Analytical Specificity/Interference:
   Analytical specificity/interference data for the CDC Human Influenza Real-Time RT-PCR Diagnostic Panel were reviewed and previously found acceptable in K243931, K200370, K190302, K172091, K153148, K141859, K130551, K111507, and K080570.

4. Assay Reportable Range:
   Not Applicable. This is a qualitative test.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):
   Data for the CDC Human Influenza Real-Time RT-PCR Diagnostic Panel were reviewed previously found acceptable in K200370, K190302, K172091, K153148, K141859, K130551, K111507, and K080570.

6. Detection Limit:
   Limit of Detection (LoD) data for the CDC Human Influenza Real-Time RT-PCR Diagnostic Panel were reviewed and previously found acceptable in K243931, K200370, K190302, K172091, K153148, K141859, K130551, K111507, and K080570. An LoD study will be conducted to evaluate the addition of a real-time PCR instrument, addition of an automated extraction instrument, addition of nucleic acid extraction reagents or manual extraction method, addition of PCR master mix, or modification of the quencher on the oligonucleotide probes, according to the established PCCP. Data demonstrating LoD equivalency will be considered acceptable to support these modifications to the device.

7. Assay Cut-Off:
   Refer to FDA Decision Summaries K200370, K190302, K172091, K153148, K141859, K130551, K111507, and K080570 for assay cut-offs FDA reviewed and previously found acceptable.

8. Carry-Over:
   Carry-over data for the CDC Human Influenza Real-Time RT-PCR Diagnostic Panel were reviewed and previously found acceptable in K200370, K190302, K172091, K153148, K141859, K130551, K111507, and K080570. A carry-over study will be conducted to evaluate the addition of a real-time PCR instrument or addition of an automated extraction instrument, according to the established PCCP. Data demonstrating pre-specified agreement with the expected results will be considered acceptable to support these modifications to the device.

B Comparison Studies:

1. Method Comparison with Predicate Device:
   Refer to the "Clinical studies" section.

2. Matrix Comparison:
   Not Applicable.

C Clinical Studies:

Clinical data for the CDC Human Influenza Real-Time RT-PCR Diagnostic Panel were reviewed and previously found acceptable in K243931, K200370, K190302, K172091, K153148, K141859, K130551, K111507, and K080570. Testing of clinical samples will be conducted to evaluate addition of a real-time PCR instrument, addition of an automated extraction instrument, addition of nucleic acid extraction reagents or manual extraction method, addition of PCR master mix, or modification of the quencher on the probes, according to the established PCCP. Data demonstrating that the performance meets or exceeds pre-specified point estimates for both positive, and negative, percent agreement (PPA and NPA), and the associated lower bounds of the 95% confidence intervals when compared to comparator will be considered acceptable to support these modifications to the device.

D Clinical Cut-Off:

Not Applicable.

E Expected Values/Reference Range:

Refer to FDA Decision Summaries K200370, K190302, K172091, K153148, K141859, K130551, K111507, and K080570 for expected values FDA reviewed and accepted previously.

VIII Proposed Change in Labeling:

If the validation studies are performed according to the specified protocols in the PCCP and the validation data meet the specified acceptance criteria established in the PCCP, the modification and supporting validation study results will be included in updated device labeling. The labeling will clearly describe the added modification(s).

IX Conclusion:

The information submitted in this premarket notification that includes PCCP for modifications to the FDA-cleared CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel VER 01 is complete and supports a substantial equivalence determination to the predicate device.