

SEP 30 2008

5. 510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

Assigned 510(k) number:
K080570

Submitted by:
Centers for Disease Control and Prevention
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Date prepared:
September 26, 2008

Device Name:
CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel

Common or Usual Name:
rRT-PCR Flu Panel

Predicate devices:
Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primer and Probe Set and the Prodesse Multiplex RT-PCR ProFlu+™ Assay

Device Description:
The CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel (rRT-PCR Flu Panel) is a panel of oligonucleotide primers and dual-labeled hydrolysis (TaqMan®) probes which may be used in real-time RT-PCR assays using the ABI 7500 Fast Dx Real-Time PCR instrument for the in vitro qualitative detection and characterization of human influenza viruses (RNA) in respiratory specimens from patients presenting with influenza-like illness (ILI). Detection of viral RNA not only aids in the diagnosis of illness caused by seasonal and novel influenza viruses in patients with ILI, but also provides

epidemiologic information on influenza and aids in the presumptive laboratory identification of specific novel influenza A viruses.

Assay Principle:

The rRT-PCR Flu Panel assay is based on real-time RT-PCR technology which is used in many molecular diagnostic assays to date. The rRT-PCR Flu Panel influenza A and B primer and probe sets are designed for universal detection of type A and type B influenza viruses. Influenza A subtyping primer and probe sets are designed to specifically detect contemporary A/H1, A/H3, and A/H5 (Asian lineage) influenza viruses in humans.

The rRT-PCR Flu Panel also includes internal positive control materials. The human RNase P (RP) primer and probe set detects human RP and is used with human clinical specimens to indicate that adequate isolation of nucleic acid resulted from the extraction of the clinical specimen. A positive result in the RP assay indicates adequate specimen was present, ensures that common reagents and equipment are functioning properly, and demonstrates the absence of inhibitory substances. A Human Specimen Control (HSC) is a noninfectious cultured human cell material that demonstrates successful recovery of RNA as well as extraction reagent integrity. The Seasonal Influenza Virus Control (SIVC) consists of three different influenza viruses representing influenza A/H1, A/H3, and influenza B viruses and cultured human cells. The SIVC demonstrates that the master mix and primer and probe sets for influenza A (InfA), influenza B (InfB), influenza A/H1 (H1), influenza A/H3 (H3), and RP are functioning properly. The Influenza Virus A/H5N1 Positive Control (H5VC) consists of a genetically modified reassortant human influenza virus (Influenza A/Vietnam/1203/04 x PR/8/34) (BSL2 category) and cultured human cells. The H5VC demonstrates that the master mix and primer and probe sets for InfA, influenza A/H5 (H5a, H5b), and RP are functioning properly. All controls (HSC, SIVC, and H5VC) are inactivated using beta-propiolactone and are noninfectious.

Intended Use:

The Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel (rRT-PCR Flu Panel) is intended for use in Real-time RT-PCR assays on an ABI 7500 Fast Dx Real-time PCR instrument in conjunction with clinical and epidemiological information:

- for qualitative detection of influenza virus type A or B in symptomatic patients from viral RNA in nasopharyngeal and/or nasal swab specimens,
- for determination of the subtype of seasonal human influenza A virus, as seasonal A/H1 or A/H3, if present, from viral RNA in nasopharyngeal and/or nasal swab specimens,
- for 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 for influenza viruses.

Performance characteristics for influenza A were established when influenza A/H3 and A/H1 were the predominant influenza A viruses in circulation. When other influenza A viruses are emerging, performance characteristics may vary.

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.

All users, analysts, and any person reporting diagnostic results from use of this device should be trained to perform and interpret the results from this procedure by a CDC instructor or designee prior to use. CDC Influenza Division will limit the distribution of this device to only those users who have successfully completed training provided by CDC instructors or designees.

Device comparison:

The rRT-PCR Flu Panel is substantially equivalent to the Prodesse Multiplex RT-PCR ProFlu+™ Assay because it utilizes real-time PCR technology to detect influenza A and influenza B in human respiratory specimens. The rRT-PCR Flu Panel further detects and differentiates influenza A/H1 and A/H3 subtypes. The rRT-PCR Flu Panel is substantially equivalent to the influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primer and Probe Set because it utilizes real-time PCR technology to detect influenza A/H5 (Asian lineage). Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primers and Probe Set and the Prodesse Multiplex RT-PCR ProFlu+™ Assay have been granted marketing clearance by the Food and Drug Administration (FDA) following 510(k) submissions. Based on clinical and analytical data, the rRT-PCR Flu Panel device has been determined to be as safe and effective and performs as well as legally marketed devices described below. The device has demonstrated clinical utility and supports the label claims.

	rRT-PCR Flu Panel	Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primers and Probe Set (K060159)	Prodesse Multiplex RT-PCR ProFlu+™ Assay (K073029)
Intended Use	Qualitative <i>in-vitro</i> detection of influenza A/H1, A/H3, A/H5 (Asian lineage), and influenza B viruses	Qualitative <i>in vitro</i> detection of influenza A/H5N1 (Asian lineage) virus	Detection/differentiation between influenza A virus, influenza B virus and respiratory syncytial virus (RSV)
Specimen Types	Nasopharyngeal or nasal swab respiratory specimens, or virus culture	Human respiratory specimens or virus cultures	Nasopharyngeal swab specimens
Technology	Real-time RT-PCR	Real-time RT-PCR	Real-time RT-PCR
Organism Detected	Influenza A/H1, A/H3, A/H5 (Asian lineage), and influenza B viruses	Influenza A virus, subtype H5N1 (Asian lineage)	Influenza type A and type B viruses, RSV
Extraction Method	<ul style="list-style-type: none"> • QIAamp® Viral RNA Mini Kit, Qiagen Inc. • Qiagen RNeasy® Mini Kit, Qiagen, Inc. • MagNA Pure LC RNA Isolation Kit II, Roche Applied Science • MagNA Pure Total Nucleic Acid Isolation Kit, Roche Applied Science 	<ul style="list-style-type: none"> • QIAamp® Viral RNA Mini Kit, Qiagen, Inc. • RNeasy® Mini Kit, Qiagen, Inc. • MagNA Pure LC Total Nucleic Acid Isolation Kit, Roche Applied Science 	MagNA Pure Total Nucleic Acid Isolation Kit, Roche Applied Science

Centers for Disease Control and Prevention
Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel
 510(k) 080570

Enzyme Master Mix	Invitrogen SuperScript™ III Platinum® One-Step Quantitative RT-PCR Kits (with or without ROX)	Qiagen QuantiTect™ Probe RT-PCR Kit, Qiagen, Inc.	Supplied in the ProFlu+™ Detection Kit
Clinical Sensitivity	> 93%	N/A*	98%
Clinical Specificity	> 90%	N/A*	83%
Required Instrumentation	Applied Biosystems 7500 Fast Dx Real-Time PCR Instrument with SDS software version 1.4	<ul style="list-style-type: none"> • Roche LightCycler® • Cepheid SmartCycler® • Applied Biosystems 7000 Sequence Detection System • Applied Biosystems Prism® 7700 Sequence Detection System 	Cepheid SmartCycler® II instrument

* Sensitivity and specificity could not be estimated due to scarcity of Asian H5 (Asian lineage) virus infections.

Performance characteristics:

1. Analytical Specificity – Inclusivity & Reactivity

The rRT-PCR Flu Panel analytical specificity was demonstrated by inclusivity and reactivity testing. The inclusivity testing utilized ten (10) influenza virus strains of A/H1N1, A/H3N2, and influenza B at low virus concentrations at or near the limit of detection (10^2 TCID₅₀/mL) to demonstrate the flexibility of the primer and probe sets to detect multiple strains of influenza virus. There were 24 influenza A/H5N1 clinical samples tested retrospectively from diverse geographic locations from suspect positive cases received at CDC. The rRT-PCR Flu Panel analytical specificity indicated 100% concordance with expected results for all primer and probe sets included in the device. This testing demonstrated that the primer and probe sets are highly specific for detecting and differentiating influenza viruses A/H1, A/H3, A/H5 and influenza B as defined previously.

Analytical Reactivity with Human Seasonal Influenza Viruses A/H1, A/H3, and Influenza B and A/H5N1 (Asian lineage) Influenza Virus

Influenza Strains Tested	Strains Detected	Expected Detection	Concordance
A/H1N1 Influenza	10 / 10	10 / 10	100 %
A/H3N2 Influenza	10 / 10	10 / 10	100 %
A/H5N1 Influenza	24 / 24	24 / 24	100 %
Influenza B	10 / 10	10 / 10	100 %

2. Analytical Specificity - Reactivity with Common Non-Influenza Respiratory Viral and Bacterial Pathogens

Analytical specificity (cross-reactivity) was evaluated by testing each primer/probe set within the device panel with nucleic acids extracted from 27 organisms (9 viruses, 17 bacteria, and 1

yeast) representing common respiratory pathogens or flora commonly present in specimens collected from the nasopharynx region. All organisms tested in this study were propagated, titered, and characterized to confirm identity prior to testing. The identity of the commensal respiratory bacteria was confirmed by 16S ribosomal RNA bi-directional sequencing. Commensal respiratory bacteria titers were determined at the CDC by standard practices. The identity of the non-influenza respiratory viruses was confirmed by bi-directional sequencing. Bacteria and yeast were tested at concentrations greater than or equal to 10^6 cfu/ml with the exception of *Mycobacterium tuberculosis* where DNA was extracted from pure culture and quantitated by spectrophotometry (0.25 ng/ μ l). Non-influenza respiratory viruses were tested at concentrations greater than 10^6 TCID₅₀/ml with the exception of human parainfluenza type 2 ($10^{3.1}$ TCID₅₀/ml due to difficulty generating a high titer virus stock in culture). Total RNA was extracted from viral cultures of Coronaviruses CoV 229E and CoV OC43 and concentrations were determined by spectrophotometry (31.6 ng/ μ l and 50.4 ng/ μ l, respectively).

Each sample (bacteria and virus) was extracted in parallel using both the Qiagen QIAamp[®] Viral RNA Mini Kit and the Qiagen RNeasy[®] Mini Kit. Each RNA sample was tested following the testing procedure previously described for the rRT-PCR Flu Panel and the Applied Biosystems 7500 Fast Real-Time PCR System. The dual extraction method was performed to demonstrate cross method equivalency and ensure no cross reactivity with the influenza primer and probe sets since negative results were expected for all samples.

Analytical Specificity with Common Non-influenza Human Respiratory Pathogens.

Markers Tested	Commensal Flora Detected	Non-Influenza Respiratory Virus Detected	Expected Detection	Concordance
Inf A	0 / 18	0 / 9	No	100 %
Inf B	0 / 18	0 / 9	No	100 %
H1	0 / 18	0 / 9	No	100 %
H3	0 / 18	0 / 9	No	100 %
H5a	0 / 18	0 / 9	No	100 %
H5b	0 / 18	0 / 9	No	100 %

3. Analytical Sensitivity – Limit of Detection

Analytical sensitivity was demonstrated by determining the limit of detection (LoD) of each primer and probe set in the rRT-PCR Flu Panel. Ten-fold serial dilutions of two different influenza virus strains of each subtype were tested to identify an end-point for detection of each primer and probe set included in the rRT-PCR Flu Panel. RNA was extracted from each of the characterized viruses with the Qiagen QIAamp[®] Viral RNA Purification kit. The LoD for each primer and probe set (InfA, InfB, H1, H3, H5a, and H5b) was calculated to determine the lowest detectable concentration range of influenza virus (EID₅₀/mL) at which $\geq 95\%$ of all replicates tested positive. The lowest concentration of influenza virus detected

was determined to be the end-point concentration where the type and subtype primer and probe sets had uniform detection. If the two end-points differed in concentration, the higher (or limiting) point was used.

Limit of Detection Summary

Influenza Virus Tested	Influenza Strain Designation	Limit of Detection (EID ₅₀ /mL)
A/H1N1	A/New Caledonia/20/1999	10 ^{1.2}
	A/Hawaii/15/2001	10 ^{1.5}
A/H3N2	A/New York/55/2004	10 ^{2.2}
	A/Wisconsin/67/2005	10 ^{1.2}
A/H5N1	A/Vietnam/1203/2004×A/Puerto Rico/8/34 reassortant (A/Vietnam/1203/2004 PR8- VN H5N1- PR8/CDC-RG)	10 ^{1.0}
	A/Anhui/01/2005×A/Puerto Rico/8/34 reassortant (A/Anhui/01/2005- PR8-IBCDC-RG5)	10 ^{1.0}
B	B/Florida/07/2004 (B/Victoria/2/87 genetic group)	10 ⁰
	B/Ohio/01/2005 (B/Yamagata/16/88 genetic group)	10 ^{0.5}

4. Clinical Performance

Performance characteristics of the rRT-PCR Flu Panel were established during a prospective study at 4 U.S. state public health laboratories during the 2006-2007 respiratory virus season (February-April). Samples used for this study were nasal and nasopharyngeal swabs collected for routine influenza testing at each site.

The reference method was rapid culture (shell vial) followed by direct fluorescent antibody screening and identification. Specimens tested at the public health testing sites followed routine diagnostic influenza rapid culture protocols and the rRT-PCR Flu Panel protocol to demonstrate performance and agreement.

A total of 415 total specimens were collected and tested at the 4 public health laboratory testing sites during the 2006-2007 influenza season for this prospective clinical study. Four hundred thirty-nine specimen results (415 prospective seasonal and 24 retrospective A/H5 influenza samples) from nasal, nasopharyngeal swabs, or cultured specimens in the case of influenza A/H5 samples were confirmed by gold standard virus culture testing. Influenza A/H5 and discrepant prospective seasonal influenza samples were further analyzed by bi-directional sequencing.

Clinical Sensitivity and Specificity Performance Summary - Prospective Specimen Testing

Analyte Tested	Sensitivity % (95% CI)	Specificity % (95% CI)
InfA	99.3 (96.1 - 99.9)	92.3 (88.5 - 94.9)
InfB	97.6 (87.4 - 99.6)	98.1 (96.2 - 99.1)
H1	93.1 (78.0 - 98.1)	99.5 (98.1 - 99.9)
H3	100.0 (96.2 - 100.0)	90.5 (86.7 - 93.3)

A formal clinical evaluation of human and/or avian influenza A/H5N1 virus was not accomplished during the CDC Clinical Evaluation Study due to the absence of suspect cases within the United States. Therefore, performance specificity and detection capability of the H5a and H5b primer and probe sets in the rRT-PCR Flu Panel could not be evaluated at the U.S. state public health laboratories during the clinical study. Retrospective data from twenty-four (24) suspect A/H5N1 positive specimens from human cases received by the CDC Influenza Division were used to demonstrate clinical performance of the H5a and H5b components of the panel.

Performance Summary - Influenza A/H5N1 Testing with Prospective and Retrospective Specimens

	Analyte Tested	Percent Positive Agreement (%)
Influenza A/H5 Positive Clinical Specimens	H5a / H5b	100 % Percent Positive Agreement (56.6% -100%) 95% CI
Influenza A/H5 Positive Cultured Specimens	H5a / H5b	100 % Percent Positive Agreement (83.2% -100%) 95% CI
Prospective Clinical Specimens	H5a / H5b	100 % Percent Negative Agreement (99.1%-100%) 95% CI

The clinical sensitivity for all markers tested was greater than 93 % and the clinical specificity for all markers was greater than 90 %. The accuracy, often referred to as percent agreement, was greater than 92 % for all markers tested.



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SEP 30 2008

Re: K080570
Trade/Device Name: Human Influenza Virus Real-time RT-PCR Detection and
Characterization Panel
Regulation Number: 21 CFR 866.3332
Regulation Name: Reagent for detection of specific novel influenza A viruses
Regulatory Class: Class II
Product Code: NXD, OEP, OCC, NSU
Dated: February 27, 2008
Received: February 29, 2008

Dear Dr. Kim:

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 (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. 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.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

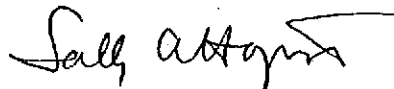
Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

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This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at 240-276-0450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at 240-276-3474. For questions regarding the reporting of device adverse events (Medical Device Reporting (MDR)), please contact the Division of Surveillance Systems at 240-276-3464. You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address <http://www.fda.gov/cdrh/industry/support/index.html>.

Sincerely yours,



Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

Centers for Disease Control and Prevention
Human Influenza Virus Real-Time RT-PCR Detection and Characterization Panel
510(k) Notification

4. Indications for Use

510(k) Number (if known): K080570

Device Name: CDC Human Influenza Virus Real-Time RT-PCR Detection and Characterization Panel

Common Name: rRT-PCR Flu Panel

The Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel (rRT-PCR Flu Panel) is intended for use in Real-time RT-PCR assays on an ABI 7500 Fast Dx Real-time PCR instrument in conjunction with clinical and epidemiological information:

- for qualitative detection of influenza virus type A or B in symptomatic patients from viral RNA in nasopharyngeal and/or nasal swab specimens,
- for determination of the subtype of seasonal human influenza A virus, as seasonal A/H1 or A/H3, if present, from viral RNA in nasopharyngeal and/or nasal swab specimens,
- for 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 for influenza viruses.

Performance characteristics for influenza A were established when influenza A/H3 and A/H1 were the predominant influenza A viruses in circulation. When other influenza A viruses are emerging, performance characteristics may vary.

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.

All users, analysts, and any person reporting diagnostic results from use of this device should be trained to perform and interpret the results from this procedure by a CDC instructor or designee prior to use. CDC Influenza Division will limit the distribution of this device to only those users who have successfully completed training provided by CDC instructors or designees.

Prescription Use X
(Per 21 CFR 801.109)

OR

Over-The-Counter Use
(Optional Format 1-2-96)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)


Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) K080570