DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20903

April 27, 2009

Rich E. Besser, MD
Acting Director
Centers for Disease Control and Prevention
1600 Clifton Road, MS C-12
Atlanta, GA 30333
Clifton, Bldg. 1, Room 6430

Dear Dr. Besser:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the Swine Influenza Virus Real-time RT-PCR Detection Panel (rRT-PCR Swine Flu Panel) for the presumptive diagnosis of swine influenza A (H1N1), pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3) by public health and other qualified laboratories.

On April 26, 2009, pursuant to section 564(b)(1)(C) of the Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency under 42 U.S.C. § 247d that affects, or has a significant potential to affect, national security, and that involves a specified biological, chemical, radiological, or nuclear agent or agents, or a specified disease or condition that may be attributable to such an agent or agents -- in this case, swine influenza A (H1N1).[1] Pursuant to section 564(b) of the Act (21 U.S.C. § 360bbb-3(b)), and on the basis of such determination, the Secretary of the Department of Health and Human Services then declared an emergency justifying the authorization of the emergency use of the Swine Influenza Virus Real-time RT-PCR Detection Panel (rRT-PCR Swine Flu Panel) subject to the terms of any authorization issued under 21 U.S.C. § 360bbb-3(a).

Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act (21 U.S.C. § 360bbb-3(c)) are met, I am authorizing the emergency use of the Swine Influenza Virus Real-time RT-PCR Detection Panel (rRT-PCR Swine Flu Panel)[2] for the presumptive diagnosis of swine influenza A (H1N1) virus infection in human individuals who have been diagnosed with influenza A caused by a virus not subtypeable by currently available FDA-cleared devices, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

[1] Memorandum, Determination Pursuant to § 564 of the Federal Food, Drug, and Cosmetic Act (April 26, 2009).
[2] FDA is authorizing the emergency use of the Swine Influenza Virus Real-time RT-PCR Detection Panel (rRT-PCR Swine Flu Panel) as described in the scope section of this letter (Section II). For ease of reference, this letter will use the term the " rRT-PCR Swine Flu Panel."

I have concluded that the emergency use of the rRT-PCR Swine Flu Panel for the presumptive diagnosis of swine influenza A (H1N1) virus infection for human individuals who are diagnosed with influenza A caused by a virus that is not subtypeable by currently available FDA-cleared devices meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

(1) The recently isolated swine influenza A (H1N1) virus can cause influenza, a serious or life threatening disease or condition to humans infected by this virus;

(2) based on the totality of scientific evidence available to FDA, it is reasonable to believe that the rRT-PCR Swine Flu Panel may be effective in the presumptive diagnosis of swine influenza A (H1N1) virus infection, and that the known and potential benefits of the rRT-PCR Swine Flu Panel, when used in the presumptive diagnosis of swine influenza A (H1N1) virus infection, outweigh the known and potential risks of such products; and

(3) there is no adequate, approved, and available alternative to the emergency use of the rRT-PCR Swine Flu Panel for the presumptive diagnosis of swine influenza A (H1N1) virus infection.[3]

Therefore, I have concluded that the emergency use of the rRT-PCR Swine Flu Panel for the presumptive diagnosis of swine influenza A (H1N1) virus infection in human individuals who are diagnosed with influenza A infections not subtypeable by currently available FDA-cleared devices meets the above criteria for issuance of an authorization.

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized rRT-PCR Swine Flu Panel for the presumptive diagnosis of swine influenza A (H1N1) virus infection for human individuals who are diagnosed with influenza A caused by a virus not subtypeable by currently available FDA-cleared devices.

The authorized rRT-PCR Swine Flu Panel is as follows:

The Swine Influenza Virus Real-time RT-PCR Detection Panel is a panel of oligonucleotide primers and dual-labeled hydrolysis (Taqman®) probes for use in the real-time RT-PCR assay on the ABI 7500 Fast Dx Real-Time PCR instrument for the *in vitro* qualitative detection of swine influenza viral RNA in nasopharyngeal and/or nasal swab specimens from patients with signs and symptoms of respiratory infection and viral culture. The universal swine influenza swInfA (NP gene) and swH1 (HA gene) primer and probe sets are designed for detection of swine A/H1N1 influenza viruses.

The rRT-PCR Swine Flu Panel includes the following primer and probe sets:

[3] No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

- **InfA** detects universal influenza A strains in nasopharyngeal and/or nasal swab specimens from patients with signs and symptoms of respiratory infection, and virus culture.
- **swInfA** specifically detects swine influenza A strains (NP gene) in nasopharyngeal and/or nasal swab specimens from patients with signs and symptoms of respiratory infection, and virus culture.
- **swH1** is specific for swine influenza A, subtype H1 (HA gene) in nasopharyngeal and/or nasal swab specimens from patients with signs and symptoms of respiratory infection, and viral culture.

The rRT-PCR Swine Flu Panel also includes control materials:

- **RNase P (RP)** detects human RNase P and is used as a positive control with human clinical specimens to indicate that adequate isolation of nucleic acid resulted from the extraction of the clinical specimen.
- **Swine Influenza Panel Real-Time RT-PCR Positive Control (SIPC)** is a positive control designed to react with all the primer and probe sets including RNase P.

The above rRT-PCR Swine Flu Panel, when labeled consistent with the attached template is authorized to be distributed to public health and other qualified laboratories[4] under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law.

The following written information pertaining to the emergency use of the authorized rRT-PCR Swine Flu Panel is authorized to be made available to health care providers and patients:

- Fact Sheet For Healthcare Providers: Interpreting Swine Influenza Rt-Pcr Detection Panel Test Results
- Fact Sheet For Patients: Understanding Swine Influenza Kit Test Results

See attached. As described in section IV below, CDC and the appropriate state and/or local public health authority(ies) are also authorized to make available additional information relating to the emergency use of the authorized rRT-PCR Swine Flu Panel that is consistent with, and does not exceed, the terms of this letter of authorization.

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the authorized rRT-PCR Swine Flu Panel in the specified population, when used in the presumptive diagnosis of swine influenza A (H1N1) virus infection, outweigh the known and potential risks of such product.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the authorized rRT-PCR Swine

[4] 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 those users who have successfully completed training provided by CDC instructors or designees. Use is limited to designated laboratories that are qualified to receive and use the CDC rRT-PCR Flu Panel (IVD) 510(K) 080570. See "Conditions of Authorization" below.

Flu Panel may be effective in the presumptive diagnosis of swine influenza A (H1N1) virus infection pursuant to section 564(c)(2)(A) of the Act. FDA has reviewed the scientific information available including the information supporting the conclusions described in Section I above, and concludes that the authorized rRT-PCR Swine Flu Panel, when used to presumptively diagnose swine influenza A (H1N1) virus infection in the specified population, meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized rRT-PCR Swine Flu Panel under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below. Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the rRT-PCR Swine Flu Panel described above is authorized to presumptively diagnose swine influenza A (H1N1) virus infection in human individuals who are diagnosed with influenza A caused by a virus not subtypeable by currently available FDA cleared devices.
This EUA will cease to be effective when the declaration of emergency is terminated under section 564(b)(2) of the Act or when the EUA is revoked under section 564(g) of the Act.

III. Waiver of Certain Requirements

I am waiving the following requirements for the rRT-PCR Swine Flu Panel during the duration of this emergency use authorization:

- current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the rRT-PCR Swine Flu Panel;
- registration and listing requirements under section 510 of the Act;
- labeling requirements for cleared, approved, or investigational devices, including labeling requirements under 21 CFR 809.10 and 809.30, except for the intended use statement (21 CFR 809.10(a)(2), (b)(2)), adequate directions for use (21 U.S.C. 352(f)), (21 CFR 809.10(b)(5) and (8)), any appropriate limitations on the use of the device including information required under 21 CFR 809.10(a)(4), and any available information regarding performance of the device, including requirements under 21 CFR 809.10(b)(12);
- investigational device requirements, including requirements under 21 CFR Part 812; and
- reporting requirements that apply to cleared or approved devices, including requirements under 21 CFR Parts 803 and 806.

IV. Conditions of Authorization

Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

CDC

A. CDC will distribute the rRT-PCR Swine Flu Panel labeled with the intended use statement, adequate directions for use, any appropriate limitations on the use of the

device, and any available information regarding performance of the device only to qualified laboratories.

C. CDC will provide to the qualified state and/or local public health authority(ies) the authorized rRT-PCR Swine Flu Panel Fact Sheets for health care providers, and the authorized rRT-PCR Swine Flu Panel Fact Sheets for patients.

D. CDC will make available on its website the authorized rRT-PCR Swine Flu Panel Fact Sheets for health care providers, and the authorized rRT-PCR Swine Flu Panel Fact Sheets for patients.

E. CDC will ensure that the state and/or local public health authority(ies) are informed of this EUA, including the terms and conditions herein.

F. CDC will ensure qualified laboratories have a process in place for reporting test results to health care providers and federal, state and/or local public health authorities, as appropriate.

G. CDC will track adverse events.

H. Through a process of inventory control, CDC will maintain records of device usage.

I. CDC will collect information on the performance of the assay, to include the incidence of false positive and negative results.

Public Health and Other Qualified Laboratories

J. Public health and other qualified laboratories will include with reports of the results of the rRT-PCR Swine Flu Panel, the authorized fact sheets for health care providers and the authorized fact sheet for patients.

K. Qualified laboratories will perform the assay on an Applied Biosystems 7500 Fast Dx Real-time PCR instrument or the RUO marketed Applied Biosystems 7500 Real-time PCR instrument that is validated by Applied Biosystems with regard to the updated software but only partially qualified regarding its laboratory performance (proficiency testing with the CDC sample panel not performed).

L. Qualified laboratories will have a process in place for reporting test results to health care providers and federal, state and/or local public health authorities, as appropriate.

CDC andstate and/or Local Public Health Authority(ies)

M. CDC and the appropriate state and/or local public health authority(ies) are authorized to make available additional information relating to the emergency use of the authorized rRT-PCR Swine Flu Panel that is consistent with, and does not exceed, the terms of this letter of authorization.

N. Only CDC may request changes to the authorized Fact Sheet for health care providers or the authorized rRT-PCR Swine Flu Panel Fact Sheet for patients. Such requests will be made by contacting FDA concerning FDA review and approval.

O. CDC and the appropriate state/and or local public health authority(ies) will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to FDA for inspection upon request.

The emergency use of the authorized rRT-PCR Swine Flu Panel as described in this letter of authorization must comply with the conditions above and all other terms of this authorization.

V. Duration of Authorization

This EUA will be effective until the declaration of emergency is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

John M. Sharf 4.27.09

Joshua M. Sharfstein, MD
Principal Deputy Commissioner
Acting Commissioner

Attachments
1. Fact Sheet For Healthcare Providers: Interpreting Swine Influenza RT-PCR Detection Panel Test Results
2. Fact Sheet For Patients: Understanding Swine Influenza Kit Test Results
3. Swine Influenza Virus Real-time RT-PCR Detection Panel (rRT-PCR Swine Flu Panel) Labeling

FACT SHEET FOR HEALTHCARE PROVIDERS: INTERPRETING SWINE INFLUENZA RT-PCR DETECTION PANEL TEST RESULTS

April 26, 2009

A public health emergency has been declared by the Secretary of Health and Human Services because of the 2009 outbreak of swine influenza A (H1N1), or "swine flu." The Food and Drug Administration (FDA) has authorized the emergency use of the Swine Influenza RT-PCR Detection Panel (rRT-PCR Swine Flu Panel) to test for the presumptive presence of swine influenza virus in clinical specimens under an Emergency Use Authorization (EUA). This authorization will terminate on April 26, 2010 or when the emergency has ceased to exist, whichever is earlier. The information in this Fact Sheet is the minimum necessary to inform you of the significant known and potential risks and benefits of the emergency use of the rRT-PCR Swine Flu Panel.

At this time, no FDA-approved/cleared tests that identify existence of swine influenza virus in clinical specimens are available in the United States. Therefore, the Centers for Disease Control and Prevention (CDC) has developed this test to detect swine influenza virus infections. Current information on swine influenza, including case definitions and infection control guidelines, is available at http://www.cdc.gov/swineflu/. All information and guidelines, including those on swine influenza virus laboratory testing, may change as we continue to learn more about this disease. Please check CDC's swine influenza virus website regularly for the most current information.

The rRT-PCR Swine Flu Panel test should be ordered to presumptively diagnose swine influenza A (H1N1) virus infection only. Nasopharyngeal or nasal swabs may be collected in the usual fashion and sent to a qualified laboratory for analysis. Specimen collection should be conducted per the clinical protocol and according to the manufacturer's instructions for the specimen collection device.

What does it mean if the specimen tests positive for swine influenza virus?
A positive test result from the rRT-PCR Swine Flu Panel indicates that the patient is presumptively infected with swine influenza virus. The test does not indicate the stage of infection. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis. For guidelines on managing patients please refer to *"Interim Guidance for Infection Control for Care of Patients with Confirmed or Suspected Swine Influenza A (H1N1) Virus Infection in a Healthcare Setting"* and *"Interim Guidance on Antiviral Recommendations for Patients with Confirmed or Suspected Swine Influenza A (H1N1) Virus Infection and Close Contacts"* at http://www.cdc.gov/swineflu/investigation.htm.

The test has been designed to minimize the likelihood of false positive test results. However, should false positive results occur, risks to patients could include a recommendation for quarantine of household or other close contacts, a recommendation for patient isolation that might limit contact with family or friends, the ability to work, or the ability to receive certain medical care, prescription of an antiviral drug or other therapy, or other unintended adverse effects.

What does it mean if the specimen tests negative for swine influenza virus?
Negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other patient management decisions. The clinical features of the illness and the type and risk of exposure are the keys to making patient management and isolation decisions. A negative RT-PCR test should not be interpreted as demonstrating that the patient does not have swine influenza virus infection, if other aspects of the patient's clinical presentation or recent epidemiologic exposures indicate swine influenza virus infection is likely, and diagnostic tests for other causes of acute respiratory illness are negative.

Contact Information for the Manufacturer:
CDC Influenza Division
1600 Clifton Road, MS-G03
Atlanta GA 30333
Contact phone 404-6390954

*Any significant new findings observed during the course of the emergency use of Swine Influenza RT-PCR assay will be made available at http://www.cdc.gov/swineflu/.

FACT SHEET FOR PATIENTS: UNDERSTANDING SWINE INFLUENZA KIT TEST RESULTS

April 26, 2009

An emergency has been declared by the Secretary of Health and Human Services because of the 2009 outbreak of swine influenza (swine flu). The Food and Drug Administration (FDA) has authorized the emergency use of Swine Influenza Test Kit to test for the presence of swine flu virus. This authorization will terminate on April 26, 2010 or when the emergency has ceased to exist, whichever is earlier. The information in this Fact Sheet is the minimum necessary to inform you of the significant known and potential risks and benefits of the emergency use of Swine Influenza RT-PCR assay.

Why was my sample tested using the Swine Influenza Test Kit?
There are no FDA cleared or approved tests that can identify swine flu virus. Therefore, your sample was tested using the Swine Influenza Test Kit because you may have been exposed to the swine flu virus. This test could help to determine whether you are infected with the swine flu virus, so that public health officials could quickly identify a case and limit its spread. The results of this test, along with other information, may also help your doctor take better care of you.

What is swine flu?
Swine flu is a respiratory disease of pigs caused by type A influenza virus that regularly causes outbreaks of influenza in pigs. Human cases of swine flu virus infection have been identified in the United States and internationally. CDC has determined that this virus is contagious and is spreading from human to human. Like seasonal flu, swine flu in humans can vary in severity from mild to severe.

What is the Swine Influenza Test Kit?
The Swine Influenza Test Kit is a sensitive test to detect the swine flu virus. The FDA has not cleared or approved this test. The FDA has agreed that we can use this test under an Emergency Use Authorization. We don't know for sure if this test can identify all people who may get sick with swine flu.

What are the known risks and benefits of Swine Influenza Test Kit?
The results of this test from nasopharyngeal or nasal swab, along with other information, can help your doctor take better care of you. Knowing your test results may help you to prevent the spread of the virus to your family or others. There may be no other benefits to you from this test.

If this test is positive, does that mean that I have swine flu?
Yes, though there is a very small chance that this test can give a result that is wrong (false positive), it is not likely. If your result from this test is positive, your doctor may decide how to care for you based on the test results along with other factors.

If this test is negative, does that mean that I do not have swine flu?
If this test is negative, you may not be sick, or you may be sick with something that is not swine flu. There is a small chance that this can give a result that is wrong (false negative). A false negative result should not affect your care. No changes in your medical care or how you interact with other people should be solely based on a negative result.

*Any significant new findings observed during the course of the emergency use of Swine Influenza Test Kit will be made available at http://www.cdc.gov/swineflu/.

******DO NOT DISCARD: Important product-specific information ******

Swine Influenza Virus Real-time RT-PCR Detection Panel (rRT-PCR Swine Flu Panel)

CATALOG: FLUSW01
LOT: 904251
EXPIRATION DATE: 04/25/2011

INTENDED USE:
The Swine Influenza Virus Real-time RT-PCR Detection 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:

- to identify patients who may be infected with swine influenza virus (A/H1N1) to allow public health authorities to respond to and limit transmission the virus during this public health emergency,
- for qualitative detection of influenza virus type A in symptomatic patients from viral RNA in human nasopharyngeal and/or nasal swab specimens,
- for presumptive identification of virus in patients who may be infected with swine influenza A subtype A/H1N1 from viral RNA in human nasopharyngeal and/or nasal swabs specimens and viral culture in conjunction with clinical and epidemiological risk factors, and
- to provide epidemiologic information for surveillance for influenza viruses.

Testing with the swine influenza swInfA and swH1 primer and probe sets should not be performed unless the patient meets clinical and epidemiologic criteria for testing suspect specimens. The definitive identification of swine influenza A/H1N1 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.

The definitive identification of swine Influenza A (H1N1) virus from patient specimens requires additional laboratory testing, along with clinical and epidemiological assessment in consultation with national influenza surveillance experts.

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.

Use is limited to designated public health laboratories and other laboratories qualified to receive and use the CDC rRT-PCR Flu Panel (IVD) K080570

REAGENTS

COMPONENT	PART NUMBER	LOT NUMBER	QUANTITY PER/VIAL	REHYDRATION VOLUME	STATE
InfA-F	MR-023	904251	20.0 nmol	0.5 ml	Lyophilized
InfA-R	MR-024	904251	20.0 nmol	0.5 ml	Lyophilized
InfA-P	MR-025	904251	5.0 nmol	0.5 ml	Lyophilized
SwInfA-F	MR-029	904251	20.0 nmol	0.5 ml	Lyophilized
SwInfA -R	MR-030	904251	20.0 nmol	0.5 ml	Lyophilized
SwInfA -P	MR-031	904251	5.0 nmol	0.5 ml	Lyophilized
SwH1-F	MR-026	904251	20.0 nmol	0.5 ml	Lyophilized
SwH1-R	MR-027	904251	20.0 nmol	0.5 ml	Lyophilized
SwH1-P	MR-028	904251	5.0 nmol	0.5 ml	Lyophilized
RP-F	MR-032	904251	20.0 nmol	0.5 ml	Lyophilized
RP–R	MR-033	904251	20.0 nmol	0.5 ml	Lyophilized
RP -P	MR-034	904251	5.0 nmol	0.5 ml	Lyophilized

Probe contains 6-FAM reporter and BHQ1 quencher. Approximate number of tests per kit: 1,000.

PRECAUTIONS:
Reagents are for investigational use only. Performance characteristics have not been established.

REHYDRATION
Rehydrate each tube with 0.5 ml (500 µl) of 10 mM Tris, pH 7.4 to 8.2 or PCR water. Dispense into aliquots.

STORAGE INSTRUCTIONS:
Prior to rehydration, store kits at 2-8°C. Store rehydrated aliquots of primers and probes at -20°C or below. Do not store in frost-free freezers. Rehydrated primers and probes may be stored frozen for up to 12 months. Thawed aliquots of probes and primers may be stored in the dark up to 6 months at 2-8°C. Do not use any product (refrigerated or frozen) past the expiration date.

PROCEDURE/INTERPRETATION/LIMITATIONS/EXPECTED VALUES:
Refer to CDC Influenza rRT-PCR Panel Flu (IVD) for instruction on using the Swine Influenza Virus Real-time RT-PCR Detection Panel provided by CDC Influenza Division. The procedure may be requested by sending email to FluSupport@cdc.gov

REAGENT COMPLAINTS/QUESTIONS:
Please send comments by email to FluSupport@cdc.gov

DISTRIBUTED BY:
Centers for Disease Control and Prevention, Influenza Division, 1600 Clifton Road, Atlanta, Georgia, 30333 USA