Guidance for Industry and FDA Staff

In Vitro Diagnostic 2009 H1N1 Tests for Use in the 2009 H1N1 Emergency

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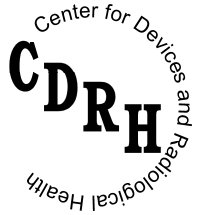

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.regulations.gov. Please identify your comments with the docket number listed in the notice of availability that publishes in the *Federal Register* announcing the availability of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This document provides guidance on the type of information and data that FDA recommends you include in an Emergency Use Authorization (EUA) request for in vitro diagnostic (IVD) devices intended for use in diagnosing 2009 H1N1 Influenza virus infections during the emergency involving Swine Influenza A[1] declared by the Secretary of the Department of Health and Human Services (HHS) on April 26, 2009 under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[2]. Such devices will be referred to in this guidance as "2009 H1N1 tests."

In accordance with the agency's Good Guidance Practice regulations, 21 CFR 10.115, you may submit comments on this guidance at any time. The agency will consider your comments and determine whether to revise the guidance at a later date.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] Swine Influenza A is now known as 2009 H1N1 Influenza (2009 H1N1).

[2] On April 26, 2009, under § 319 of the Public Health Service Act (42 U.S.C. § 247d), the Acting Secretary of HHS determined that a public health emergency exists involving Swine Influenza A. On the basis of this determination, pursuant to § 564(b) of the FD&C Act (21 U.S.C. 360bbb-3(b)), the Deputy Secretary declared an emergency justifying the authorization of the emergency use of certain in vitro diagnostics for detection of Swine Influenza A.

2. Scope

This document applies to 2009 H1N1 tests while the declaration of emergency under § 564(b) of the FD&C Act concerning 2009 H1N1 Influenza (H1N1) is in effect. See 21 U.S.C. 360bbb-3(b)(2) regarding the termination of a declaration of emergency. FDA is issuing this level 1 guidance for immediate implementation consistent with the agency's good guidance practices regulation (21 CFR 10.115). FDA has determined that prior public participation is not feasible or appropriate (21 CFR 10.115(g)(2)) because the agency must act immediately to protect the public health during the declared emergency concerning 2009 H1N1 Influenza. The guidance represents FDA's policy for 2009 H1N1 tests that are already being offered for clinical use on the date the guidance is issued, as well as for any new 2009 H1N1 tests. The information contained in this guidance document should facilitate the submission of EUA requests for 2009 H1N1 tests to FDA by those who wish to pursue such requests.

3. Background

The definition of a device is set forth at section 201(h) of the FD&C Act. It provides in relevant part: "The term 'device' . . . means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals . . ." (21 U.S.C. 321(h)(2)). IVD products for human use are devices and, as such, they are subject to regulation by FDA.

During a declared emergency under Section 564(b)(1) of the FD&C Act, public health authorities must take measures to prepare for, respond to, and contain the emergency. Diagnostic devices are an essential and critical element of public health protection; it is imperative that those managing the public health response are assured of the performance of the devices used to diagnose the disease or condition associated with the emergency.

Under Section 564 of the FD&C Act, the Commissioner, acting under delegated authority from the Secretary of HHS, may issue an Emergency Use Authorization (EUA) authorizing the emergency use of an unapproved or uncleared device, or an unapproved or uncleared use of an approved or cleared device. Before an EUA may be issued, the Secretary of HHS must declare an emergency justifying the authorization based on one of three determinations: a determination of a domestic emergency, or a significant potential for a domestic emergency, by the Secretary of Homeland Security; a determination of a military emergency, or a significant potential for a military emergency, by the Secretary of Defense; or a determination of a public health emergency by the Secretary of HHS. See 21 U.S.C. § 360bbb-3(b)(1). In the case of a determination by the Secretary of HHS, the Secretary must determine that a public health emergency exists under section 319 of the Public Health Service (PHS) Act 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 agent or agents. Based on such a determination, the Secretary of HHS may then declare an emergency that justifies the EUA, at which point the Commissioner may issue an EUA if the criteria for issuance of an authorization under section 564 of the FD&C Act are met. These criteria include that the device may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by the biological, chemical, radiological, or nuclear agent, the known and potential benefits of the device outweigh its risks, and there is no adequate, approved, and available alternative. An EUA does not constitute clearance or approval by FDA.

On April 26, 2009, pursuant to section 564(b)(1)(C) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of HHS determined that there is a public health emergency under the Public Health Service Act § 319 (42 U.S.C. § 247d) that affects, or has a significant potential to affect, national security, and that involves a specific biological, chemical, radiological, or nuclear agent or agents – in this case, 2009 H1N1 virus. On the basis of this determination, on April 26, 2009, the Secretary declared an emergency justifying the authorization of the emergency use of certain in vitro diagnostic devices for detection of 2009 H1N1 virus.

The 2009 H1N1 virus continues to spread throughout the US and globally, and while most people infected do not have severe disease, the virus can cause substantial morbidity and mortality, particularly in pregnant women and children and adults with underlying medical conditions.

All EUAs will be terminated when the emergency declaration justifying them is terminated. The declaration of emergency will expire in one year, on April 26, 2010, unless it is extended or terminated earlier. Manufacturers should seek premarket clearance or approval for H1N1 tests before termination of an EUA.

4. FDA Regulation of 2009 H1N1 Tests

While FDA encourages submission of premarket notifications (510(k)s) for all 2009 H1N1 tests, the agency is aware that during a declared emergency, it may not be possible for manufacturers of 2009 H1N1 tests to generate complete clinical validation data that would normally be included in a 510(k) for influenza testing prior to distributing or offering a test. A manufacturer may not be able to test the usual number of specimens needed for a 510(k) within the short period of time available to address the acute need for test capacity. Additionally, appropriate validation specimens may not be available in certain areas at the time the test is needed. If manufacturers of 2009 H1N1 tests are unable to submit a 510(k) and there is a continued public health need for 2009 H1N1 tests during this declared emergency, then before distributing such tests, manufacturers should submit an EUA request to FDA.

Sponsors wishing to submit 510(k)s for 2009 H1N1 tests should refer to the guidance document entitled “Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Reagents for Detection of Specific Novel Influenza A Viruses”

(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078583.htm) for guidance on what types of information and data should be included in the submission. Tests cleared under a 510(k) will be subject to general controls and all established controls for class II devices of this type (Reagents for detection of specific novel influenza A viruses, 21 CFR 866.3332).

In order to facilitate the submission of EUA requests for 2009 H1N1 tests to FDA by those who wish to pursue such requests, the Agency is issuing this guidance document to inform stakeholders of the type of data and information FDA believes should be included in an EUA request for devices intended to reliably detect 2009 H1N1 Influenza virus during this declared emergency. FDA is committed to reviewing EUA submissions in an expedited manner, when feasible and while there is a continued public health need for 2009 H1N1 tests during this declared emergency.

5. EUA Requests for 2009 H1N1 Influenza Tests

When reviewing an EUA request for an IVD, FDA considers the scientific evidence of test performance, as well as the risks and benefits of each test when used to detect 2009 H1N1 Influenza virus or to be used as a first step in an algorithm for the identification of 2009 H1N1. 21 U.S.C. § 360bbb-3(c).

This guidance document describes the information and performance validation data FDA recommends to include in an EUA request for 2009 H1N1 tests.

We recommend that you address, in this order:

- administrative information,
- limited manufacturing source and quality information,
- specifics about how the test works and its exact intended use,
- how the test is interpreted,
- analytical sensitivity (limit of detection) data,
- analytical specificity (reactivity/inclusivity and cross-reactivity) data,
- data demonstrating performance of the test against a comparator using limited clinical specimen numbers, including clinical study protocol,
- description of risks of collecting specimens,
- explanation of benefits of the test, and how false positives are minimized,
- description of how risks are mitigated by other factors,
- provision of a fact sheet for healthcare providers and patients,
- information on how a laboratory can obtain instructions or clarifications on proper test use or test procedure (if a commercially distributed device),
- names of contact(s) for healthcare providers and patients to report adverse events that may be related to the test,
- complete package insert, and
- references to published literature relevant to your test.

For ease of use, the guidance provides standardized text, with brackets indicating where the requestor should provide information and the type of information requested. A number of examples of information are provided to assist the user in determining what information to furnish. Requestors should replace text in brackets with the requested information and delete examples provided before submitting the request to FDA.

EUA Submissions for 2009 H1N1 Tests

This section is intended to facilitate organization and submission of information on 2009 H1N1 tests. It is written to capture the majority of 2009 H1N1 tests, but it may be adapted to account for a device's specific characteristics, where applicable. When providing information under this section, you should replace bracketed text with your test-specific information. Examples are provided to assist in choosing the appropriate language but are not intended to be comprehensive. Please select or provide the appropriate text and delete the remainder of the example. While this section provides recommendations for EUA requests, you should explain omissions of information described in this section or the decision to deviate from the recommendations of this section. The unexplained omission of information described in this section may delay review of your submission, or may lead to denial of your request.

The EUA letters of authorization, fact sheets, and product labeling for devices authorized during the 2009 H1N1 influenza emergency are found at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm**.**

A. PURPOSE FOR SUBMISSION

Emergency Use Authorization (EUA) request for distribution of the [**test name**] in/to [**CLIA High Complexity Laboratories/authorized laboratories/qualified laboratories/other (explain)]** for the *in vitro* qualitative detection of human influenza A viruses and the differential detection of the 2009 H1N1 influenza virus in [**nasopharyngeal swabs (NPS), nasal swabs (NS), throat swabs (TS), and nasal aspirates (NA), other respiratory specimens (describe)]** from patients with signs and symptoms of respiratory infection.

B. MEASURAND

[Describe what your test specifically measures, and the influenza types and subtypes detected]

[**Example language for a nucleic-based acid test (NAT):** *Specific influenza virus nucleic acids target sequences detected* [**if applicable**] *are* [**conserved region of the matrix (M) gene from influenza A viruses, H1, N1, other (describe)**]. *This test detects influenza types/subtypes* [**list the influenza types and subtypes detected]**

C. APPLICANT

[**Your complete contact information and information for any additional contact you authorize, if any**]

D. PROPRIETARY AND ESTABLISHED NAMES

Proprietary Name- [**Official or marketing name of your test**]
Established Name- [**Common or scientific name of your test**]

E. PRODUCT DESCRIPTION

1. [**Briefly describe the technology of the test and how this technology works to identify the measurand, the instruments employed/required to perform the test from sample collection to result, and the specimen types for which you claim to have specific performance characteristics as described below**]

2. [**Briefly describe, in order, the steps required to perform the test**]

3. The [**test name**] test uses the following:

   [**If applicable, list all primer and probe sets or specific antigens/antibodies and briefly describe what they detect**]

4. Control material to be used with the [**test name**] test includes:

   [**List all control materials and briefly describe what they are, how they are expected to work, and where in the testing process they are used.** If a control is commercially available, provide supplier's name and catalog number or other identifier.]

F. TEST PRINCIPLE:

1. **[Describe the test's scientific principle/methodology and the purpose of the controls. Describe the test's experimental process and the purpose of each component (primer and probe /antigen-antibody sets if applicable). Explain for what purpose and when the test should be used.]**

   [**Example language for a nucleic acid-based PCR test:** *The* [**test name***] is a real-time reverse transcription polymerase chain reaction (rRT -PCR) test. The* [**name/label**] *primer and probe set is designed for detection of type A influenza virus in humans. The 2009 H1N1 influenza virus primer probe set* [**name/label**] *is designed to specifically detect 2009 H1N1 influenza virus in humans.*

   One-step RT-PCR assays are one-tube assays that first reverse-transcribe specific RNA templates into cDNA copies. This cDNA then undergoes a polymerase chain reaction (PCR) that utilizes a thermocyclic heating and cooling of the reaction to logarithmically amplify a specific region of DNA. The probe anneals to a specific target sequence located between the forward and reverse primers. During the extension phase of the PCR cycle, the 5' nuclease activity of Taq polymerase degrades the probe, causing the reporter dye to separate from the quencher dye, generating a fluorescent signal. With each cycle, additional reporter dye

molecules are cleaved from their respective probes, increasing the fluorescence intensity. Fluorescence intensity is monitored at each PCR cycle.]

2. A "no template" (negative) control is needed to [**describe need**] and is used [**describe use**]

3. A positive template control is needed to [**describe need**] and is used [**describe use**]

4. An extraction control [**describe control**] is needed to [**describe need**] and is used [**describe use**]

G. INTENDED USE

[**Provide the specific intended use of your test**]

[**Example language for a nucleic acid test (NAT):** [**Test name**] is *intended for use in* [**CLIA High Complexity Laboratories/authorized laboratories/qualified laboratories/other (describe)**] *using the* **[name of instrument system]** *for the in vitro qualitative detection of influenza virus and identification of 2009 H1N1 influenza virus viral RNA* [**if applicable**] *in* [**nasopharyngeal swabs (NPS), nasal swabs (NS), throat swabs (TS), nasal aspirates (NA), other respiratory specimens (describe)**] *from patients with signs and symptoms of respiratory infection in conjunction with clinical and epidemiological risk factors.*
Testing with the [**test name**] *should not be performed unless the patient meets clinical and epidemiologic criteria for testing suspect specimens. The identification of 2009 H1N1 influenza should be performed along with a clinical and epidemiological assessment.*

Negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other patient management decisions.]

H. UNMET NEED ADDRESSED BY THE PRODUCT

[There are several 2009 H1N1 tests that have received marketing authorization under an EUA during this declared emergency. You should include a list of currently approved/cleared/available tests (current at the time of your submission) in your discussion. See http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm for the current "available" test list.]

[**Describe the unmet need addressed by your test**]

[**Example text:** *A public health emergency has been declared by the Secretary of Health and Human Services because of the outbreak of the 2009 H1N1 influenza virus. Additionally the World Health Organization (WHO) raised the pandemic alert level to*

Phase 6 on June 11, 2009. [**Briefly describe why this test is needed given that EUA authorization has already been issued for other tests**.]

Example description*: This EUA is designed to utilize the* [**test name**] *to expand testing capabilities during the public health emergency. If authorized, it would provide an alternative diagnostic tool to* [**specify the end user**] *for the detection of the 2009 H1N1 influenza virus, which would help meet the public demand for and relieve the burden of influenza testing currently performed by the Public Health laboratories and other diagnostics centers*.]

I. APPROVAL/CLEARANCE STATUS:

The [**test name**] has been validated according to [**certifying, licensing, or accreditation organization (describe)**] requirements for use in the [**CLIA High Complexity Laboratories/authorized laboratories/qualified laboratories/other (describe)**]. The test is not cleared, approved, or subject to an approved investigational device exemption.

J. PRODUCT MANUFACTURING:

1. The product will be manufactured at [**manufacturer's name**] by [**manufacturer name**] personnel consistent with practices for the production of **[types of devices]** based on [**type of quality system**]**.** Material manufactured by [**manufacturer's name**] may be packaged by [**packager name**] manufacturing facility.

2. Components manufactured by [**manufacturer's name**] and supplied with the test include:

   [**List all components and reagents provided for your test, including volumes, concentrations, quantities, etc.**]

3. Components required but not included with the test:

   [**List all components and reagents not included with the test that must be supplied by the user to perform the test, with specific supplier names and catalog numbers or other identifiers for obtaining these components and reagents**].
   [**If applicable, include the primer and probe sequences used in the test in a table format similar to the example below**].

Label Name	**Description**	**Oligonucleotide Sequence (5'>3')**	**nmol per Vial**
Ex. XYZ Inf A-F	*Univ XYZ Forward Primer*		*20.0*

4. The [**test name**] has been validated using only the components referenced above. The [**test name**] was developed using [**describe briefly the primers and probes, and or antigens and antibodies used in the test and their performance in the detection of 2009 H1N1 Influenza virus].**

5. [**Briefly describe current sample throughput capacity, total time required to perform the test (from clinical specimen collection to result), and number of tests that can be performed per instrument run and per day. Also, describe if and how overall testing capacity will be increased by use of your test**].

K. ADEQUATE, APPROVED, CLEARED, AND AVAILABLE ALTERNATIVES

[Discuss the lack of approved/cleared/and available products for this purpose. Note that although other tests are "available" under an EUA (see section H), these are not approved or cleared.]

L. INTERPRETATION OF RESULTS

All test controls should be examined prior to interpretation of patient results. If the controls are not valid, the patient results cannot be interpreted.

1. [**Test name**] Positive and Negative Controls

   [**Describe in detail the use conditions and measured values (if applicable) for valid and invalid positive and negative controls. Also, describe when control results indicate that outcomes can and cannot be reported**.]

2. Examination of Patient Specimen Results:

   [**Describe when clinical specimen test results should be assessed and the criteria for test validity**.]

   [Example text: *Assessment of clinical specimen test results should be performed after the positive and negative controls have been examined and determined to be valid and acceptable.*]

3. Interpretation of Results:

   [**Clearly indicate how to interpret numeric test values (if applicable) as positive or negative for presence of the 2009 H1N1 influenza virus, seasonal influenza A, etc. Indicate how to identify indeterminate results (if they exist)**

and how the user should resolve them. Also describe if and when repeat testing may be required.]

[**When applicable, provide a table clearly describing the possible combinations of test result values for each primer/probe or antigen/antibody set, and how they should be combined and interpreted for your test.]**

M. SAFETY AND EFFECTIVENESS

1. Analytical Performance:

Analytical Sensitivity/ Limit of Detection (LoD):

Analytical sensitivity LoD studies determine the lowest detectable concentration of influenza virus at which approximately 95% of all (true positive) replicates test positive. The LoD was determined for [**list each primer and probe set or antigen/antibody set (if applicable) for your test**] by limiting dilution studies using characterized samples.

[List the titers and strains of the viral stocks used for the LoD study, and describe how the stocks were prepared and how the titers were determined.]

[**List the dilution factor and number of serial dilutions**] of the characterized influenza viruses that were tested to identify an end-point for detection with each primer and probe set. The viral RNA was extracted [**if applicable to your device**] with [**nucleic acid extraction/purification method**] from each of the serial dilutions. (Note: a serial dilution of extracted viral RNA is not acceptable).

Serial dilution of the characterized influenza viruses were then tested in **[number of replicates (three-five recommended)]** replicates. The lowest concentration at which all [**number of replicates**] replicates were positive was treated as the tentative LoD for each test. The LoD of each test was then confirmed by testing [**number of replicates** (**at least 20 recommended)**] with concentrations at the tentative limit of detection. The final LoD of each test was determined to be the lowest concentration resulting in positive detection of [**number of positive replicates (at least 19 out of 20 replicates**)]

Summary of LoD data **[include a table for each viral strain tested]:**

[Example Table for nucleic acid-based tests**:]**

Virus Strain Tested	Analyte Tested	Stock Virus Titer	Serial 10-Fold Dilution Factor	TCID 50/mL Dilution Tested	Call Rate	Run 1 C_t	Run 2 C_t	Run 3 C_t	Run 4 C_t	Run 5 C_t	Avg. C_t (n=5)	Lowest Concentration with Uniform Positivity per Analyte	Limit of Detection (LoD) per Virus Strain
Example: *A/Iowa/1/2006*	*IVD Inf A*	*10^9 $TCID_{50}$/mL*	*10e3*	*$10^{6.0}$*	*5/5*	*26.50*						*$10^{3.0}$ $TCID_{50}$/mL (36.19 Ct)*	*$10^{3.0}$ $TCID_{50}$/mL*
			10e4	*$10^{5.0}$*	*5/5*	*30.40*							
			10e5	*$10^{4.0}$*	*5/5*	*34.21*							
			10e6	*$10^{3.0}$*	*5/5*	*36.70*							
			10e7	*$10^{2.0}$*	*4/5*	*0.00*							

[**Include analysis of LoD results, indicating the final LoD for each test**.]

2. Analytical Specificity:

The analytical specificity of **[test name**] was evaluated with respect to:

a) Reactivity (inclusivity) with a number of swine influenza and other influenza virus strains.

[*Example Table:*]

			# detected by [*your test name*]	
Specimen Tested	Titer	# Tested	[*primer name*] primer	[*primer name*] primer
Ex. Human Swine H1N1				
Swine H1N1				
Human Swine H1N2				
Swine H1N2				
Swine H3N2				

[**NOTE:** We recommend that you demonstrate that your test can detect the strains mentioned above at viral levels at or near the LoD. Other strains recommended for inclusivity studies can be found in reference 1. It is highly recommended that seasonal influenza A (H1N1) and seasonal influenza A (H3N2) also be included in the inclusivity study if you claim influenza type A detection**.]**

The [**test name**] was able to detect [**names of detected strains**]. The [**primer and probe names**] primer/probe [**if applicable**] appeared specific for [**appropriate strain names**].

b) Potential cross-reactivity with seasonal human influenza viruses and other respiratory pathogens.

Cross-reactivity of the [**test name**] was evaluated using other human respiratory pathogens and seasonal influenza viruses at [**list pathogens and seasonal influenza viruses and include titers of the organisms tested; we recommend that you test medically relevant levels of viruses and bacteria (usually 10^6 cfu/ml or higher for bacteria and 10^5 pfu/ml or higher for viruses)**].

[Example language for a nucleic acid-based test: *Genomic RNA of different organisms was extracted using* [**extraction method name**] *and assayed to show* [**some/much/no**] *cross-reactivity of each primer and probe set* [**if applicable**] *with nucleic acids of other organisms.* [**Briefly describe cross-reactivity, if any, confirmation procedure, and final results. Also, provide a table specifying the organisms tested and appropriate results/data. A list of suggested organisms is available in reference 1.**]]

3. Clinical Studies:

The [**test name**] performance characteristics were established by comparing clinical study results with the [**comparator name**] results.

[**Describe the comparator used to evaluate your test's performance.]**

[Note: Acceptable comparator methods are:

- the CDC rRT -PCR Swine Flu Panel,
- other EUA authorized tests,
- high performance nucleic acid- based FDA cleared tests for detecting influenza A followed by PCR plus sequencing of flu A positive samples[3]**,**
- high performance nucleic acid- based FDA cleared tests that specifically detect the 2009 H1N1virus, and
- viral culture followed by PCR plus sequencing of positive samples[3].**]**

[3] The LoD of the PCR used should be determined if you use PCR plus sequencing as part of your comparison. We recommend that you perform the sequencing reaction on both strands of the amplicon (bi-directional sequencing) and demonstrate that the sequence method is capable of generating least 200 consecutive base pairs of an acceptable quality (e.g., a quality score of 20 or higher as measured by PHRED or similar software packages). The sequence results must match the reference or consensus sequence in order to establish agreement with the comparator.

[Example table for primers if sequencing is used:]

Influenza Target	Primer Sequence	Gene	Amplicon (bp)

[**NOTE:** We suggest that clinical performance be demonstrated by testing, at a minimum, 10-20 clinical specimens positive by an acceptable comparator and 50-100 specimens confirmed negative by an acceptable comparator.]

[Briefly describe the clinical study protocol; describe how and where the specimens were obtained, number of specimens tested, specimen types, and study results. For nucleic acid based tests, describe the viral RNA extraction process, reverse transcription, RT-PCR amplicon generation, primers used, and purification of amplified DNA. Describe the testing by an acceptable comparator. If bi-directional sequencing is a component of acceptable comparator testing, describe the validation parameters of the sequencing results (if applicable) and include details of systems used.]

[EXAMPLE TABLE FOR CLINICAL PERFORMANCE DATA:]

SUMMARY OF CLINICAL PERFORMANCE EVALUATION

		[*CDC assay or other EUA authorized 2009 H1N1 influenza virus assay or bi-directional sequencing*]			
		2009 H1N1 Influenza virus Positive	2009 H1N1 Influenza virus Negative	Total	
[*Your test name*]	2009 H1N1 Influenza virus Positive				___ % Positive Agreement 95% CI (___% - ___%)
	2009 H1N1 Influenza virus Negative				___ % Negative Agreement 95% CI (___% - ___%)
	Total				

[**Prepare a table for each specimen type tested**.]

N. RISKS AND BENEFITS:

1. Risks

   False positives:

   The [**test name]** has been designed to try to minimize the likelihood of false positive test results. However, should false results occur, they may present risks to patients:

   - The patient could be isolated resulting in less contact with medical staff, family or friends. While such measures may likely already be in place for symptomatic persons meeting the case definitions, based on current CDC guidelines there is a small chance that this could occur even for mildly ill or asymptomatic persons who test positive.
   - An antiviral drug or other therapy may be unnecessarily prescribed. Such treatments might have unintended adverse effects.
   - A false positive result in the context of the current public health emergency could lead to misallocation of resources used for surveillance and prevention.
   - Although a negative test result does not rule out influenza, a false negative has the potential to result in a delay or lack of treatment. This would prevent a patient from obtaining the potential benefits of antiviral therapy, such as reduced severity and duration of illness and may potentially result in significant harm or even death. For these reasons, clinical decisions to initiate treatment should be made based on patient characteristics and clinical assessment and should not be delayed while waiting for test results.
   - **[Describe any additional risks applicable to your test.]**

   The risks of collecting specimens are as follows:

   [**Describe risks of collecting specimens using your recommended procedure.]**

2. Benefits

   The chief benefit associated with the [**test name**] is the availability, where needed and appropriate, of reliable testing of human specimens for the 2009 H1N1 influenza virus.

   True positive results provide confirmatory support for the diagnosis of a 2009 H1N1 influenza virus infection. True positive results may add information supporting the decision, which in most cases should be made even before testing

is available based on clinical assessment, to begin treatment with antiviral medications. Waiting for test results should not delay decisions to initiate therapy. Also, establishing the 2009 H1N1 influenza virus as the true cause of the patient's symptoms may prevent further workup for other possible causes and save healthcare resources.

True negative results may benefit both physicians and patients by allowing other possible illnesses to be pursued

[Explain any additional benefits of your test.]

3. Measures Taken to Mitigate Risk or Optimize Benefits:

[**Explain how the submitted test works to optimize benefits and minimize false positives/negatives**.]

4. Risk-Benefit Assessment

To date, validation testing results indicate that the [**test name**] can meet the current need for 2009 H1N1 influenza virus testing by providing dependable results from human specimens that are positive (or presumptively positive as appropriate) for 2009 H1N1 influenza virus.
Risk of false positive or negative results with the [**test name**] is expected to have been mitigated by demonstrating analytical performance (analytical sensitivity and specificity) and clinical performance with clinical specimens comparable to the [**CDC H1N1 influenza RT-PCR assay, other EUA authorized test, or high performance FDA cleared tests for the flu A marker followed by PCR plus bi-directional sequencing of flu A positive samples.**]

The risks posed by use of the [**test name**] are mitigated by:

- limited distribution to [**Example: CLIA High Complexity Laboratories/authorized laboratories/qualified laboratories/other (describe)]**
- oversight of public health experts in emergency response activities
- use of the [**test name**] in conjunction with other laboratory, epidemiological, and clinical evaluation tools

Based on these factors, the potential benefits from the use of the **[test name**] are expected to outweigh the risks.

O. FACT SHEET FOR HEALTHCARE PROVIDERS AND PATIENTS:

[Provide fact sheets for healthcare providers and patients]

[Examples of fact sheets:

Focus Diagnostics Influenza A H1N1 (2009) Real Time RT-PCR assay - http://www.focusdx.com/focus/cms/cms.asp?pid=h1n1

CDC rRT-PCR Swine Flu Panel - http://www.cdc.gov/h1n1flu/eua/testkit.htm]

P. INSTRUCTIONS FOR USE:

Refer to [**website/package insert**] for instruction on using the [**test name**] provided by [**company name**]. The procedure may be requested by contacting [**list who should be contacted, and how to contact them to request the instructions**].

Q. RECORD KEEPING AND REPORTING INFORMATION TO FDA:

[**Company**] will distribute the [**test name**] to [**Example: CLIA High Complexity Laboratories/authorized laboratories/qualified laboratories/other (describe)]** to test respiratory tract samples. Final results will be reported to the healthcare provider through [**Example: CLIA High Complexity Laboratories/authorized laboratories/qualified laboratories/other (describe)].** The submitting health care provider will be responsible for communicating test results to the patient with the appropriate interpretation.

Healthcare providers and patients will be requested by [**manufacturer name]** to report adverse device effects to [**contact name**] at [**email/contact information**].

R. PROPOSED LABELING/PACKAGE INSERT:

[Include proposed package insert labeling.]

[Examples of package inserts (for Nucleic Acid Tests):

Focus Diagnostics Influenza A H1N1 (2009) Real Time RT-PCR assay
http://www.fda.gov/downloads/MedicalDevices/Safety/EmergencySituations/UCM173517.pdf

CDC rRT-PCR Swine Flu Panel
http://www.fda.gov/downloads/MedicalDevices/Safety/EmergencySituations/UCM161598.pdf]

S. REFERENCES:

1. "Establishing Performance Characteristics of In Vitro Diagnostic Devices for Detection or Detection and Differentiation of Influenza Viruses." FDA: 15 February 2008. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079171.htm

2. "Guidance - Emergency Use Authorization of Medical Products" at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm

3. "Novel H1N1 Flu (Swine Flu)" http://www.cdc.gov/H1N1FLU

4. "Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Reagents for Detection of Specific Novel Influenza A Viruses" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078583.htm

5. "Medical Devices and Flu Emergencies" http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm.