Executive Summary

Proposed Reclassification of the Rapid Influenza Detection Tests

CDRH Microbiology Devices Advisory Committee Meeting

June 13, 2013

Gaithersburg, Maryland

Table of Contents

Introduction 3

Background 4

Regulation of *In Vitro* Diagnostic Devices 4

Regulation of Currently Marketed Devices for the Detection of Influenza 8

Risks Associated with Influenza Diagnostic Test Systems 11

Current Status of Influenza Testing 12

Purpose of Reclassification 13

Scope 14

Proposed Special Controls 14

Minimum Sensitivity Criteria 14

Reference Method 20

Monitoring of Device Performance over Time 20

Provisions for a Public Health Emergency 21

Effect of a Change in Classification on the Diagnostic Industry 21

Summary 23

Questions for the Panel 24

Appendices 25

Appendix A 26

References 26

Appendix B 29

Additional References 29

Appendix C 30

From FDA Website 30

Introduction

The Division of Microbiology Devices in the Center for Devices and Radiological Health at FDA has regulatory oversight of diagnostic assays for influenza. FDA is convening this Advisory Panel meeting to discuss the regulation of rapid influenza detection tests (also referred to as antigen tests) that are currently regulated as Class I devices.

The recent 2009 flu pandemic has emphasized the poor performance of the rapid influenza detection tests (RIDTs) as they were widely used by clinicians in point of care settings. At that time, FDA received informal communications from CDC and public health laboratories reporting the poor performance of these devices with anecdotal reports of many misdiagnosed cases of influenza, some with serious or fatal outcomes.

The first influenza virus detection methods using enzyme immunoassay technology (EIA) were cleared for the market in the late 1970's, at the time when the only other method for the detection of the virus was viral culture. The first RIDT for use directly from clinical specimens was cleared in 1990, followed by others in the late 1990's. There are approximately 12 RIDTs on the market today. The first RIDT was CLIA waived in the year 2000, which facilitated its use in a physician's office, outside of a clinical laboratory. Currently, there are six CLIA waived RIDTs on the market that are widely used. Although the poor sensitivity of RIDTs has always been a concern, they were valued for their ease of use, quick time to result and high positive predictive value due to their high specificity.

In recent years, many studies have been published showing the poor sensitivity of the RIDTs when compared to viral culture and to reverse transcription polymerase chain reaction (RT-PCR) (see references). According to these reports, the performance of RIDTs has often not matched the specifications provided in test labeling. As the rapid influenza tests are widely used by physicians to diagnose influenza infection, FDA, CDC and BARDA are very concerned about the negative impact the use of these tests has on public health, particularly during a pandemic, such as occurred in 2009.

The purpose of the meeting is to discuss the proposed reclassification of the rapid antigen tests for the detection of influenza virus, currently regulated as Class I devices, into Class II. The discussion will include the proposed special controls FDA believes would ensure that these devices are safe and effective through their Total Product Life Cycle (TPLC).

The sections below provide an overview of the following topics as background for the meeting:

- Device class categories
- Existing classification regulations for influenza devices
- FDA reclassification process
- Reasons for the proposed reclassification

Further, FDA will discuss the proposed mitigations to the risks associated with the influenza devices subject to the proposed reclassification:

- Issues to be addressed by special controls
- Proposed special controls
- Consequences of the reclassification on the diagnostic industry
- Perceived benefits of the reclassification

The last section contains specific questions to the Panel Members pertaining to this proposed reclassification. Attached to this document is a list of relevant references and copies of published articles that are particularly informative.

Background

Regulation of *In Vitro* Diagnostic Devices

Per 21 CFR 809.3, *in vitro* diagnostic devices are:[1]

> "Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended …for use in the collection, preparation, and examination of specimens from the human body."

FDA regulations applicable to *in vitro* diagnostic devices are based on the FDA classification of the device. The current approach to classification is a product of several laws, most prominently the 1976 Medical Device Amendments to the original Food, Drug and Cosmetic Act (the FD&C Act) (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/). Medical devices, including *in vitro* diagnostic devices, are classified based on the level of risk to patients.
The three regulatory classes for device categorization are based on the level of control necessary to assure the safety and effectiveness of a device:

- Class I: Devices of low risk for which general controls are sufficient to provide a reasonable assurance of safety and effectiveness of the device.
- Class II: Devices which require both general and special controls to provide a reasonable assurance of safety and effectiveness of the device.
- Class III: Devices for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness.

[1] All citations or references to the Code of Federal Regulations in this document are available at: http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm.

Class I Devices

Class I devices are primarily those devices for which general controls are determined to be sufficient to provide reasonable assurance of device safety and effectiveness. Class I devices may also be devices that do not present a potential unreasonable risk of illness or injury. General controls are controls not unique to any specific device but controls that can be applicable to devices in general. Examples of general controls include:

- Registration of manufacturing facilities and listing of products;
- 510(k) premarket notification requirement;
- Good manufacturing practices (GMPs);
- Quality System procedures that provide for notification of risks and of repair, replacement, or refund;
- Restrictions on sale and distribution or use; and
- Other regulatory controls, e.g., labeling, adverse event reporting, misbranding, adulteration of the device.

For example, multipurpose culture medium is a Class I device as specified in the Code of Federal Regulations:

21 CFR 866.2300 Multipurpose culture medium.

(a) *Identification*. A multipurpose culture medium is a device that consists primarily of liquid or solid biological materials intended for medical purposes for the cultivation and identification of several types of pathogenic microorganisms without the need of additional nutritional supplements. Test results aid in the diagnosis of disease and also provide epidemiological information on diseases caused by these microorganisms.

(b) Classification. Class I (general controls).

The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in 866.9.

Due to their low risk, FDA has exempted almost all Class I devices (with the exception of reserved devices) from the 510(k) requirement, including those devices that were exempted by final regulation published in the Federal Registers of December 7, 1994, and January 16, 1996. If a manufacturer's device falls into a generic category of exempted Class I devices, then a 510(k) submission and FDA clearance are not required before marketing the device in the U.S. However, these devices have not been exempted from other general controls (e.g., registration and listing, GMP regulations, etc.). Further, all devices exempt from the premarket notification requirement are only exempt as long as they do not exceed the limitations to their exemption. Limitations to exemptions for microbiology devices are found in 21 CFR 866.9. Of these limitations on exemptions, an exemption especially relevant to many of microbiology diagnostic devices is 21CFR 866.9(c)(6) “For identifying or inferring the identity of a microorganism

directly from clinical material"(21 CFR 866.9(c)(6)), as many of them are intended to be used directly from clinical specimens.

Further, although all manufacturers of medical devices are subject to the Quality System Regulation (21 CFR Part 820), FDA has exempted almost all Class I devices (with the exception of five types of devices listed in 820.30(a)(2), none of which are *in vitro* diagnostic devices) from the design controls requirement. As a result, all influenza detection tests regulated as Class I devices are not subject to design controls requirements. The intent of the design controls regulation is to implement processes and procedures to allow for identifying deficiencies in the design input requirements in early stages of the development of a device. Design controls also apply to all changes to the device or manufacturing process design, including those occurring long after a device has been introduced to the market. These changes are part of a continuous, ongoing effort to design, develop and make available a device that meets the needs of the user and/or patient.

Class II Devices

Class II devices are those that cannot be classified as Class I because general controls alone are insufficient to provide reasonable assurance of device safety and effectiveness, but where there is sufficient information to establish special controls, in addition to general controls, that can provide such assurance. Examples of special controls may include:

- performance standards;
- post-market surveillance;
- patient registries;
- guidelines;
- design controls; and
- other appropriate action deemed necessary for mitigating the risks of the device.

For example, a culture medium intended to determine whether a particular organism is susceptible to a drug that can be used to treat a bacterial infection is a Class II device as specified in the Code of Federal Regulations:

21 CFR 866. 1700 Culture medium for antimicrobial susceptibility tests.

(a) *Identification.* A culture medium for antimicrobial susceptibility tests is a device intended for medical purposes that consists of any medium capable of supporting the growth of many of the bacterial pathogens that are subject to antimicrobial susceptibility tests. The medium should be free of components known to be antagonistic to the common agents for which susceptibility tests are performed in the treatment of disease.
(b) *Classification.* Class II (performance standards).

Class I reserved (non-exempt) and Class II submissions are reviewed by FDA under what is referred to as the 510(k) process. Under the 510(k) paradigm, a device can be cleared for marketing if it is determined to be as safe and effective as a preexisting 'predicate' device (the device is 'substantially equivalent' to the predicate device).[2] Substantial equivalence broadly encompasses the following:

- The new device has the same intended use as the predicate and the new device has the same technological characteristics as the predicate,

  or
- The new device has the same intended use as the predicate but the new device has different technological characteristics and the information submitted to FDA *and* the device both (a) does not raise new questions of safety and effectiveness and (b) the sponsor demonstrates that the device is at least as safe and effective as the legally marketed device.

As described on the FDA web site, "a claim of substantial equivalence does not necessarily imply that the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable." The determination of 'substantial equivalence,' is therefore a multifaceted examination of the new device focused heavily on the intended use and not independent of the underlying technology.[3]

Class III Devices

Class III devices are those for which insufficient information exists to determine that general and special controls can provide reasonable assurance of the safety and effectiveness, or where these devices are life sustaining or life supporting, of substantial importance in preventing impairment of human health, or present unreasonable risk of illness or injury. Class III devices require, in addition to general controls, a pre-market approval' (PMA) application for which additional materials are necessary at the time of regulatory filing by the sponsor/manufacturer. FDA has greater oversight over Class III than over Class II and Class I devices.[4]

The discussion at this meeting will be focused on the differences between Class I and Class II requirements for medical devices and the FDA level of oversight. As described above, the major distinction between these two classes of devices is that Class II regulation allows for special

---

[2] Devices which are submitted under a 510(k) are 'cleared' for marketing by FDA; under the PMA process (described below) devices are 'approved' by FDA.

[3] More detailed information regarding pre market applications under the 510(k) process is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm, reproduced as an attachment to this document.

[4] More detailed information regarding pre market PMA applications is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm, reproduced as an attachment to this document.

controls that are necessary to provide a reasonable assurance of the safety and effectiveness of the device. Additionally, all Class II devices are subject to design controls requirements.

Regulation of Currently Marketed Devices for the Detection of Influenza

Currently there are three regulations governing influenza detection devices:

21 CFR 866.3330 Influenza virus serological reagents:

> (a) Identification. Influenza virus serological reagents are devices that consist of antigens and antisera used in serological tests to identify antibodies to influenza in serum. The identification aids in the diagnosis of influenza (flu) and provides epidemiological information on influenza. Influenza is an acute respiratory tract disease, which is often epidemic.
>
> (b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in § 866.9.

To date, all methods utilizing antigens and antibodies as components of the device have been regulated under 21 CFR 866.3330. This was the first influenza device regulation to be established. Early influenza tests consisted of laboratory methods to detect antibodies that develop in response to influenza infection. As enzyme immunoassay technology developed, tests capable of detecting viral proteins (antigens) directly in human respiratory samples were cleared by FDA starting in 1978. Since then, numerous influenza detection tests based on antigen-antibody binding properties were developed and cleared for the market. Those devices were placed under this classification regulation and include:

a) Rapid antigen tests intended for use in near-patient settings

   These tests are based on chromatographic immunoassay technology, typically designed in a simple to use format for the qualitative detection of influenza A and B viral nucleoprotein antigens directly from respiratory specimens. The results of the test can usually be obtained in less than 30 minutes.

   (e.g., BinaxNOW Influenza A&B (Alere), Directigen EZ Flu A+B (BD), QuickView Influenza A+B (Quidel) and more recently Veritor System for Flu A+B (Becton Dickinson) and Sofia Influenza A+B FIA (Quidel) and others)

b) Direct Specimen Fluorescent Antibody tests performed directly on clinical specimens (DSFA) intended for use in high complexity laboratories

These tests utilize specific antibodies, labeled with fluorescein, which are directed against influenza viral proteins (antigens). These tests require trained personnel and specialized equipment (a fluorescence microscope) to interpret the results.

(e.g. D3 FastPoint L-DFA Influenza A/Influenza B Virus Identification Kit (Diagnostic Hybrids), Bartels Viral Respiratory Screening and Identification Test (Intracel Corp.)

c) Direct Fluorescent Antibody tests performed on cultured isolates (DFA) also intended for use in high complexity laboratories.

(e.g., D^3 Duet DFA Influenza A/Respiratory Virus Screening Kit (Diagnostic Hybrids))

21 CFR 866.3332 Reagents for detection of specific novel influenza A viruses

(a) Identification. Reagents for detection of specific novel influenza A viruses are devices that are intended for use in a nucleic acid amplification test to directly detect specific virus RNA in human respiratory specimens or viral cultures. Detection of specific virus RNA aids in the diagnosis of influenza caused by specific novel influenza A viruses in patients with clinical risk of infection with these viruses, and also aids in the presumptive laboratory identification of specific novel influenza A viruses to provide epidemiological information on influenza. These reagents include primers, probes, and specific influenza A virus controls.

(b) Classification. Class II (special controls). The special controls are:

(1) FDA's guidance document entitled "Class II Special Controls Guidance Document: Reagents for Detection of Specific Novel Influenza A Viruses." See § 866.1(e) for information on obtaining this document.

(2) The distribution of these devices is limited to laboratories with experienced personnel who have training in standardized molecular testing procedures and expertise in viral diagnosis, and appropriate biosafety equipment and containment.

To date, all devices intended for the detection of specific novel influenza A subtypes have been regulated under 21 CFR 866.3332. These include:

a) Devices for the detection of Novel Influenza A Virus, A/H5 (Asian Lineage) RNA (e.g., Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primer and Probe Set (CDC))

b) Devices for the detection of Novel Influenza A virus, A/H5 NS1 Protein (e.g.,AVantage™ A/H5N1 Flu Test (Arbor Vita Corp.)

c) Devices for the detection of 2009 H1N1 Influenza Virus (Swine Origin), Nucleic Acid or Antigen
(e.g., Simplexa™ Influenza A H1N1 (2009) (Focus Diagnostics, Inc.))

21 CFR 866.3980 Respiratory viral panel multiplex nucleic acid assay

(a) Identification. A respiratory viral panel multiplex nucleic acid assay is a qualitative *in vitro* diagnostic device intended to simultaneously detect and identify multiple viral nucleic acids extracted from human respiratory specimens or viral culture. The detection and identification of a specific viral nucleic acid from individuals exhibiting signs and symptoms of respiratory infection aids in the diagnosis of respiratory viral infection when used in conjunction with other clinical and laboratory findings. The device is intended for detection and identification of a combination of the following viruses:

(1) Influenza A and Influenza B;
(2) Influenza A subtype H1 and Influenza A subtype H3;
(3) Respiratory Syncytial Virus subtype A and Respiratory Syncytial Virus subtype B;
(4) Parainfluenza 1, Parainfluenza 2, and Parainfluenza 3 virus;
(5) Human Metapneumovirus;
(6) Rhinovirus; and
(7) Adenovirus.

(b) Classification . Class II (special controls). The special controls are:

(1) FDA's guidance document entitled "Class II Special Controls Guidance Document: Respiratory Viral Panel Multiplex Nucleic Acid Assay;"
(2) For a device that detects and identifies Human Metapneumovirus, FDA's guidance document entitled "Class II Special Controls Guidance Document: Testing for Human Metapneumovirus (hMPV) Using Nucleic Acid Assays;" and
(3) For a device that detects and differentiates Influenza A subtype H1 and subtype H3, FDA's guidance document entitled "Class II Special Controls Guidance Document: Testing for Detection and Differentiation of Influenza A Virus Subtypes Using Multiplex Nucleic Acid Assays."

The influenza detection devices regulated under 21 CFR 866.3980 consist of assays intended to simultaneously detect and identify nucleic acids of multiple viruses in human respiratory specimens or viral culture. Assays for influenza typing and subtyping may also be components of a respiratory viral panel. A manufacturer must follow the Special Controls Guidance Document which includes identification of the studies and other information a manufacturer must submit to FDA to address the issues of safety and effectiveness for multiplex devices and provides minimum performance criteria for sensitivity and specificity.

There are currently 11 manufacturers who hold a 510(k) for devices that detect influenza as part of a respiratory panel of microorganisms.

(e.g., xTAG™ Respiratory Viral Panel (Luminex Diagnostics Inc.), ProFlu+ Assay (Hologic Corp.), and Verigene Respiratory Virus Plus Nucleic Acid Test (Nanosphere Inc.))

Risks Associated with Influenza Diagnostic Test Systems

In vitro diagnostic devices for the detection of influenza viruses are important for establishing the diagnosis of influenza in patients with respiratory illness in order to provide appropriate patient treatment. Early diagnosis of influenza can reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. Additionally, accurate and early diagnosis of influenza provides valuable information regarding the presence of influenza viruses in the community and contributes to better management and control of influenza outbreaks in the community. Establishing the performance of these devices in controlled studies and understanding the risks that might be associated with the use of these devices is critical to their safe and effective use.

Although an influenza test that detects influenza viruses is intended for use as an aid in the diagnosis of influenza infection in conjunction with clinical symptoms and other laboratory findings, failure of the device to perform as indicated (producing erroneous or inaccurate results) could mislead the physician and cause inappropriate or delayed medical treatment of a patient. Failure of the test to produce accurate test results can also lead to inaccurate epidemiological information that may contribute to inappropriate public health responses.

Specifically, a false negative result may lead to failure to provide a correct diagnosis and the appropriate treatment of infection caused by influenza virus and may contribute to unnecessary treatment for another suspected condition. A false negative result will also provide incorrect epidemiological information leading to failure to initiate appropriate corrective measures to control and prevent additional infections.

A false positive result on the other hand may lead to delayed treatment of a respiratory infection caused by another etiologic agent, which could potentially result in a more serious patient outcome. A false positive result will also provide incorrect epidemiological information on the presence of influenza in a community, which may result in unnecessary patient isolation or contact limitations and in unnecessary close contact investigations.

A lack of result due to a device malfunction also may lead to a delayed diagnosis and an inadequate treatment regime and, again, lead to delayed epidemiological information on the presence of influenza in a community.

It is important to note that additional testing (e.g., bacterial culture, immunofluorescence, and chest x-rays/radiography) and clinical information are recommended in order to obtain a final diagnosis of influenza infection.

Current Status of Influenza Testing

Historically, many of the rapid influenza antigen detection tests (RIDT) that were cleared since 1998 demonstrated less than desirable performance (good specificity but low sensitivity). Today, these devices can be used by manufacturers as predicates in a 510(k) submission which, under the 510k process of demonstrating performance equivalence to an already cleared predicate or reference device, promotes further clearance of devices that do not meet the needed performance for detection and management of infection by novel strains of influenza.

Currently, the rapid influenza antigen detection tests are the most widely used diagnostics for influenza, especially in outpatient settings (Landry, 2011). These tests are easy to use, provide results in 10-30 minutes and are relatively inexpensive, aiding in the prescribing of antivirals in the relatively small window of effectiveness (1-2 days after onset of symptoms). Initially, many of these tests were cleared for the market when no other diagnostics were available and there was a need for tests to help physicians in the rapid differential diagnosis of influenza infection. Although most of the rapid antigen tests cleared for the market prior to 2008 had sub-optimal sensitivity, they demonstrated high specificity and were considered to be of benefit due to their high positive predictive value.

It is well known that the performance of these tests is highly dependent on such factors as proper sample collection, transport and storage conditions if testing is performed at another facility, and time from illness onset to sample collection. As the viral load is highest within the first 48 hours of illness and then decreases with time during the course of infection (Cheng et al., 2009; Esposito et al., 2011; Loeb et al., 2012; Talbot et al., 2010), the timing of the sample collection is crucial for optimal test performance. Because RIDTs require 10^4 to 10^6 infectious influenza particles for detection, they perform best in young children who shed high titers of the virus (Esposito et al., 2011).

Although these tests are simple, careful attention to the proper test procedure instructions and specimen sampling is essential as there is ample opportunity for error. A large study conducted early during the 2009 pandemic in New York reported an alarmingly low sensitivity of one particular RIDT (Ginocchio et al., 2009b; Landry, 2011). As this appeared to be atypical, it could have possibly been related to poor sample quality and inexperienced personnel as the demand for testing rapidly increased at that time (Landry, 2011).

It is well established that influenza viruses have a propensity for mutation and recombination of the genome. The influenza virus genome is made up of eight segments of negative stranded RNA. The genome is replicated by the PA, PB1 and PB2 proteins from segments of the same name. Since the RNA polymerase is very error prone, introducing numerous nucleotide

substitutions during replication, it promotes rapid evolution and immune evasion in the structure of the virus. Small changes in the nucleic acid sequences result in antigenic drift, which may cause the functional components of influenza diagnostic devices not to recognize current influenza strains (Higgins et al., 2010). Another consideration is antigenic shift, as seen in all of the past pandemics since 1918. Antigenic shift occurs when one or more of the eight genome segments are re-assorted in the currently circulating virus strain with a viral strain typically found in animal species. Antigenic shift often results in a novel influenza virus that has not previously infected humans. Many of the diagnostic tests for influenza detect the nuclear protein (NP), which is one of the more conserved proteins in the virus and may be less likely to undergo antigenic drift. However, re-assortment can occur with the NP segment which is likely to introduce significant antigenic changes in the NP protein. Therefore, these changes may affect the ability of any influenza diagnostic device to detect the viral antigens or the viral RNA of currently circulating influenza strains. The emergence of the 2009 H1N1 strain highlighted the concern that changes in the antigenicity and in the nucleic acid sequences may affect the performance of influenza detection assays. As a result of the 2009 pandemic, it became clear that reliable influenza tests are of utmost importance to effectively implement a strategy to contain influenza during a pandemic.

Purpose of Reclassification

This panel meeting has been convened for the specific purpose of discussing the proposed reclassification of influenza detection devices that fall under 21 CFR 866.3330 and as such are regulated as Class I devices. The discussion at this meeting will be focused on whether influenza diagnostic devices currently regulated as Class I devices should remain in Class I or be reclassified into Class II. Due to the issues presented here and the elevated concerns associated with influenza diagnostics in the context of the recent 2009 H1N1 pandemic as well as human infections with two novel influenza viruses within the last two years (the swine H3N2v variant and the avian H7N9), FDA believes that general controls are not sufficient and reclassification of RIDTs into Class II is needed to mitigate the known risks associated with RIDRs. Since special controls cannot be established under the current Class I classification regulation, FDA proposes to establish a new classification regulation with addition of special controls.

It is important to note that although most Class I diagnostic devices are exempt from the premarket notification requirement (as described in the section above), the rapid influenza antigen tests exceed the limitations to the exemption because they are intended "For identifying or inferring the identity of a microorganism directly from clinical material"(21 CFR 866.9(c)(6)). Therefore, the manufacturers of these tests are currently required to submit a 510(k) application to FDA even though they are classified as Class I devices.

Based on the collective knowledge of the poor clinical performance of the rapid influenza tests along with the increased understanding of the genetic variation of influenza viruses, we believe that the proposed special controls for these devices should address: 1) the minimum acceptable performance criteria, 2) an appropriate reference method to demonstrate the performance in

support of a 510(k) clearance, 3) at a minimum, annual monitoring of analytical reactivity after the product is cleared for market, as well as testing of newly emergent strains of influenza with the potential to cause a public health emergency, e.g., a significant outbreak or even a pandemic.

Scope

FDA is considering a reclassification of all rapid influenza detection devices currently regulated under 21 CFR 866.3330 into Class II with special controls. The proposed reclassification regulation, if finalized, would apply to all rapid influenza diagnostic devices currently regulated as Class I under part 866.3330. If reclassified, all currently marketed as well as new rapid influenza detection devices based on the immunoassay technology and seeking FDA clearance, would be subject to the new regulation when finalized.

The Fluorescent Antibody tests, whether intended for use directly with clinical specimens (DSFAs) or with viral culture material (DFAs) will remain under the existing regulation and will continue to be regulated as Class I devices. Since DSFAs are used in a laboratory environment rather than in point of care settings, they would remain in Class I due to the lower risk level associated with these tests.

Influenza molecular tests will continue to be regulated under the two existing Class II regulations for influenza devices, 21 CFR 866.3332 and 21 CFR 866.3980. If the proposed special controls are recommended by the Panel, FDA will update the special controls for the respiratory viral panel multiplex nucleic acid assay regulation (21 CFR 866.3980) to include a requirement for annual monitoring of analytical reactivity with the contemporary influenza strains for any multiplex assay with an influenza detection component.

Proposed Special Controls

Based on discussions, both internally and in collaboration with CDC and BARDA, FDA focused on four issues related to the performance of RIDTs that we believe need to be addressed. The proposed special controls have also been developed based on our review of published literature concerning the performance of rapid antigen tests, as well as the collective scientific knowledge and experience of the three public health agencies.

Minimum Sensitivity Criteria

In order to develop a requirement for the minimum acceptable sensitivity and specificity criteria for RIDTs, we reviewed the performance as presented in the FDA cleared device labeling of all RIDTs cleared for market in the U.S. since 1998 (16 devices in total). We have only focused on the sensitivity measures of performance, as the specificity of these devices has been consistently very high and not an issue of concern. These sensitivity estimates were derived by combining the data from all prospectively conducted clinical studies in support of a 510(k) submission for

all specimen types combined. Results from testing of samples not prospectively collected (retrospective) were not included in our calculations.

Table 1 summarizes the device sensitivity performance for influenza A and influenza B demonstrated in clinical studies submitted in support of FDA clearance for each of the 16 devices.

Table 1. Rapid Influenza Diagnostic Tests (RIDTs) FDA Cleared Since 1998 Currently Marketed in the US								
K041441	**Device**	**510k Number**	**Date of FDA Clearance**	**Comparator**	**Flu A Sensitivity Point Estimate**	**95% CI**	**Flu B Sensitivity Point Estimate**	**95% CI**
Beckton Dickinson	BD Veritor System for Flu A+B	K121797	9/7/2012	NAT	81.30%	70.0% - 88.9%	85.60%	76.8% - 91.4%
Beckton Dickinson	BD Veritor System for Flu A+B	K120049	4/16/2012	NAT	83.00%	78.0% - 87.0%	81.30%	72.1% - 88.0%
Beckton Dickinson	BD Veritor System for Flu A+B	K112277	10/28/2011	NAT	83.60%	78.2% - 87.9%	81.30%	74.8% - 86.4%
Quidel	Sofia Influenza A+B FIA	K112177	10/24/2011	Culture	94.20%	91.0% - 96.3%	89.50%	85.3% - 92.6%
Alere	Clearview Exact II	K092349	1/6/2011	Culture	94.00%	83.0% - 98.0%	77.00%	67.5% - 85.0%
Princeton BioMeditech	BioSign Flu A+B	K083746	11/10/2010	Culture	92.60%	86.1% - 96.2%	86.60%	76.4% - 92.8%
Response Biomedical	RAMP Influenza A/B	K071591	4/16/2008	Culture	80.20%	71.8% - 86.5%	76.20%	54.9% - 89.4%
Meridian	True Flu	K071657	11/15/2007	Culture	86.60%	79.1% - 91.7%	60.20%	50.3% - 69.3%
Binax	BinaxNOW Influenza A&B	K062109	11/9/2006	Culture	80.70%	76.2% - 84.5%	64.70%	47.9% - 78.5%
Genzyme Corp.	OSOM Influenza A&B	K051244	2/21/2006	Culture	73.80%	64.4% - 81.9%	60.00%	45.2% - 73.6%
Beckton Dickinson	Directigen EZ Flu A+B	K042472	7/7/2005	Culture	86.60%	82.6% - 89.8%	75.60%	67.4% - 82.2%
SA Scientific	SAS FluAlert Influenza A and Influenza Ba	K041439	7/22/2004	Culture	76.00%	65.2% - 84.3%	90.50%	71.1%- 97.4%
Quidel Corp.	QuickVue Influenza A+B Test	K031899	9/11/2003	Culture	80.50%	73.7% - 85.9%	70.10%	61.3% - 77.6%
Remel	Xpect Influenza A/B	K031565	7/17/2003	Culture	92.20%	84.0% - 96.4%	97.80%	88.7% - 99.6%
Beckton Dickinson	Directigen EZ Flu A+B	K001364	6/28/2000	Culture	86.20%	81.2% - 90.1%	82.40%	69.7% - 90.4
Quidel Corp.	QuickVue Influenza A/B Test	K991633	9/24/1999	Culture	74.80%	66.9% - 81.4%	This assay detects both Flu A and Flu B, but does not differentiate between the two subtypes.	

[a] SAS FluAlert Influenza A+B (K080380) was cleared on 7/23/09 based on performance data against the FDA cleared SAS FluAlert Influenza A and FluAlert Influenza B tests (K041439 and K041441) as the comparator. Therefore it is not included in the table.

Table 1 above shows that the sensitivity estimates for the rapid influenza detection devices cleared since 1998 have a broad range of clinical performance:

Influenza A

Lowest:	73.8% (95% CI: 64.4% - 81.9%)
Highest:	94.2% (95% CI: 91.0% - 96.3%)

Influenza B

Lowest:	60.0% (95% CI: 45.2%-73.6%)
Highest:	97.8% (95% CI: 88.7% - 99.6)

We also reviewed numerous published scientific reports on the subject of performance of these devices. The information presented in Table 2 is a result of an extensive literature search in PubMed. From approximately 100 English language articles on influenza diagnostics published in the last five years, 15 articles were selected for further review. In this review we included only studies performed in the United States that focused primarily on the performance of rapid antigen influenza tests and that were deemed to be free of bias. Again, since the specificity of the RIDTs has been consistently high and not an issue for concern, we focused on the data describing test sensitivity. In most cases, the sensitivity was listed in the source article; when it was not, the sensitivity was calculated as (the number of true positives) / (the number of true positives + the number of false negatives). Many studies did not separate positive results of influenza A from positive results of influenza B, but only described results for overall "influenza detection". For this reason, we combined the data for influenza A and B when they were reported separately to calculate an overall measure of performance for influenza.

For the purpose of comparison, we also presented, for each device, the sensitivity observed in the studies submitted in the 510(k) for FDA clearance, using samples obtained during the year the device was evaluated. For consistency, the sensitivity estimates are also presented by combining the data for influenza A and B, as was done for the information obtained from literature.

The data presented in Table 2 shows the performance of six commonly used rapid antigen tests as reported in multiple studies conducted between 2002 and 2010 (Gordon et al., 2010; Rahman et al., 2008; Cruz et al., 2010; Sambol et al., 2010; Biggs et al., 2010; Gordon et al., 2009; Sandora et al., 2010; Vasoo et al., 2009; Ginocchio et al., 2009b; Ginocchio et al., 2009a; Landry et al., 2008; Mehlmann et al., 2007; Poehling et al., 2006; Lu et al., 2012; Louie et al., 2010; 2009; Uyeki et al., 2009). We listed the year when each of the published studies was conducted to compare the performance described in these studies with that of the studies included in each specific device 510(k) submission. The differences in performance for the same device evaluated during different years may be explained by variability in performance when the dominant circulating virus changed, as was the case during the 2009 pandemic. All measures of sensitivity are presented with the associated 95% confidence interval.

Table 2. Sensitivities of RIDTs in the Studies Submitted in 510(k)s to Support Pre-market Clearance of a Device and as Reported in Post-market Published Studies

	510(k) STUDY				LITERATURE			
MANUFACTURER	SEASON	REFERENCE METHOD	SENSITIVITY (COMBINED FLU A + FLU B)	95% CONFIDENCE INTERVAL	SEASON	REFERENCE METHOD	SENSITIVITY (COMBINED FLU A + FLU B)	95% CONFIDENCE INTERVAL
1	2005-2006	Culture	79.3	74.9 - 83.0	2006-2007	RT-PCR or Culture	34.5	0 - 85.8
					2006	RT-PCR	48.5	40.5 - 65.4
					2009	Culture and/or 2 RIDT	40.5	23.2 - 56.3
					2009	Culture, and/or Respiratory Viral Panel and / or 2 RIDT	10.4	6.9 - 15.4
					2009	RT-PCR	38.3	27.1 - 51.0
					2009	RT-PCR	59.6	52.6 - 66.3
					2006-2007	RT-PCR	47.7	4.3 - 84.0
					2009-2010	Luminex xTAG	93.9	77.7 - 98.6
					2009	Culture	55.5	51.9 - 58.9
					2009	RT-PCR	45.0	43.3 - 46.3
2	2003-2005	Culture	85.2	80.6 - 88.9	2009	RT-PCR	46.7	34.6 - 59.1
3	1999	Culture	78.4	67.7 - 86.2	2009	RT-PCR	53.3	40.9 - 65.4
					2008	RT-PCR (Nicaragua ILI Criteria)	68.5	63.4 - 73.3
					2008	RT-PCR (CDC ILI Criteria)	72.1	66.3 - 77.5
					2009-2010	Luminex xTAG	100.0	92.7 - 100
					2009	RT-PCR	65.8	61.1 - 70.3
					2010	RT-PCR	64.1	53.5 - 73.9
	2005	Culture	73.4	65.2 - 80.3	2002-2004	Culture or 2 Consecutive PCR	82.0	69.0 - 92.0
					2005-2006	RT-PCR	85.0	74.0 - 92.0
					2005-2006	Culture	93.0	83.0 - 97.0
					2007-2008	Culture	28.7	20.0 - 39.5
					2007-2008	RT-PCR	24.8	19.4 - 31.0
4	2003	Culture	94.3	88.7 - 97.2	2009	RT-PCR	46.9	33.7 - 60.0
					2009-2010	Luminex xTAG	92.3	62.2 - 98.9
5	2006-2007	Culture	74.3	68.0 - 79.7	2009-2010	Luminex xTAG	100.0	79.9 - 100
6	2006-2007	Culture	79.5	71.9 - 85.5	2009	Culture and/or 2 RIDT	78.3	60.4 - 93.3
					2009	Culture, and/or Respiratory Viral Panel and / or 2 RIDT	41.2	26.4 - 57.8

Study where sensitivity falls below 95% CI for A+B stated in labeling

The literature review of studies conducted using commercially available RIDTs revealed the following issues of concern:

a. Studies conducted in the US between 2002 and 2010, showed that the sensitivity of RIDTs commercially available at that time ranged from 25% to 100%.
b. Several studies showed that the sensitivity of RIDTs was highly dependent on the viral load of the specimen tested and that they failed to identify influenza cases where other non-RIDT methods were able to detect the presence of the virus in a specimen.
c. Although all RIDTs have been cleared for market with a limitation that all negative results should be followed up with viral culture, it is common knowledge that many physicians do not use the tests as intended, i.e., do not follow up with culture (Cunha et al., 2010).

Although the data was collected under various conditions, it clearly shows that many of the RIDTs, currently in broad usage, perform inadequately and cannot be relied on to provide accurate sensitivity information to aid in the diagnosis of an influenza infection. Therefore, FDA believes that a requirement for a minimum acceptable sensitivity for any device intended for the detection of influenza viruses should be one of the special controls associated with the proposed regulation.

The proposed minimum clinical performance criteria were developed with consideration of the enzyme immunoassay technology used to manufacture most RIDTs, as compared to more recent molecular techniques. Therefore, we propose two sets of minimum performance criteria for these devices, depending on the comparator used in the evaluation of clinical performance. Specifically, a manufacturer of an RIDT used for diagnostic purposes should demonstrate the following minimum sensitivity and specificity for their device when compared to a reference method (or percent agreement when compared to an acceptable comparator method):

a. When compared to viral culture as the reference method :

Sensitivity

Flu A Point estimate of 90% with 80% lower bound of the 95% confidence interval
Flu B Point estimate of 80% with 70% lower bound of the 95% confidence interval

Specificity

All influenza detection devices should demonstrate specificity with a lower bound of the 95% confidence interval exceeding 90% for both, Flu A and Flu B.

b. When compared to a molecular comparator method:

Sensitivity

Flu A Point estimate of 80% with 70% lower bound of the 95% confidence interval
Flu B Point estimate of 80% with 70% lower bound of the 95% confidence interval

Specificity

All influenza detection devices should demonstrate a specificity estimate with a lower bound of the 95% confidence interval exceeding 90% for both, influenza A and influenza B.

The proposed criteria for sensitivity are based on the performance of rapid influenza devices cleared in the last 5 years and the majority of these devices meet the proposed criteria.

Reference Method

We have also considered the comparators that have been used to establish the performance criteria of influenza detection devices. All devices before 2008 sent to the FDA for review were cleared based on a comparison with viral culture as a reference method when evaluated in clinical studies that supported a 510(k) clearance. Although viral culture has been considered a "gold standard" reference method for influenza viruses for decades, it is subject to variability in testing protocols as well as the skill of laboratory personnel performing this methodology. Because viral culture protocols are not standardized, performance of the rapid antigen tests demonstrated during a 510(k) study in support of clearance may have been biased due to inconsistencies and poor performance of a particular reference influenza culture procedure. As technology has evolved, newer methods for influenza virus detection based on nucleic acid amplification have been developed. There are currently a number of FDA cleared molecular-based assays available for the detection of influenza nucleic acids; these newer tests are gradually replacing viral culture as a method of choice in many microbiology laboratories. As FDA has acquired significant knowledge concerning the performance of influenza molecular based tests, we have come to recognize many nucleic acid amplification tests (NAATs), in addition to viral culture methods, as suitable comparators for establishing the performance of a new diagnostic device for influenza. Although the sensitivity of these molecular methods has surpassed the sensitivity of the enzyme immunoassay (EIA) based methods and they are frequently used as predicate devices, virus propagated in culture in accordance to a well-established protocol performed by well trained technicians, is still considered to be a useful reference method for detecting antigen in properly collected specimens. FDA believes that a requirement for using a currently appropriate comparator method(s) in evaluating the performance of a new influenza detection device is crucial in ensuring that the performance of these devices to detect influenza improves over time.

Monitoring of Device Performance over Time

Another issue of great concern to the scientific community is the genetic drift characteristic of the influenza virus. As stated above, the ability to recognize influenza virus antigens or nucleic acid sequences in a diagnostic device is subject to the evolutionary changes of the virus. FDA believes that annual testing of the analytical reactivity of influenza tests with contemporary circulating viruses is an important and reasonable requirement to ensure that available influenza diagnostic tests maintain their ability to detect influenza virus over the lifetime of the device's Total Product Life Cycle (TPLC). Therefore, a manufacturer of any influenza diagnostic device that detects influenza viral antigens or influenza viral gene segments (protein or nucleic acid), either in single unit test formats or multi-test formats, should conduct annual analytical testing of their device with contemporary strains, including current vaccine strains, based on the information made available by WHO and CDC and following a standardized protocol.

Elements of the proposed protocol include testing a standardized panel of viruses selected in coordination with FDA. Three dilutions of viral stocks at clinically relevant concentrations

between 10^2 and 10^5 $TCID_{50}$/mL should be tested. Each dilution should be tested in triplicate. To claim detection, the device would have to be positive with all replicates at least at one dilution. Standardized panels of well characterized viral stocks could possibly be available from CDC. Alternatively, the stocks could be obtained from commercial vendors. The testing could be conducted in-house or at a contract laboratory. Absence of analytical reactivity would be reflected in labeling as a limitation.

In addition, FDA is proposing to update the existing special controls for the Respiratory Viral Panel regulation (21 CFR 866.3980) with a special control requirement to conduct annual monitoring of analytical reactivity with contemporary influenza strains for any multiplex assay with an influenza detection component.

Provisions for a Public Health Emergency

Finally, variants of influenza virus sometimes emerge unexpectedly, as in 2009 when a novel reassortant influenza virus resulted in human-to-human transmission and a pandemic. In such a situation rapid detection and characterization of novel influenza viruses remain critical components of national efforts to prevent further transmission and subsequent cases. Since RIDTs can provide quick test results, they become very useful. However, it is important to know whether the available influenza diagnostic tests can effectively detect the new virus before using an RIDT in such a situation. Therefore, FDA believes that if a public health emergency or a potential for a public health emergency is declared by the Secretary of HHS, manufacturers must test the analytical reactivity of their influenza detection device with the novel influenza virus as soon as samples become available.

Effect of a Change in Classification on the Diagnostic Industry

If the rapid influenza detection devices, currently regulated as Class I devices, were to be reclassified into Class II, all devices of this type currently on the market will be subject to the new requirements at the time the reclassification rule goes into effect and will have to meet the following requirements:

1. Minimum clinical performance criteria; currently marketed devices not meeting performance criteria must be withdrawn from the market one year after the rule is finalized;
2. Implementation of Design Controls;
3. Annual testing of analytical reactivity with contemporary influenza viruses;
4. Testing of newly emergent influenza viruses if a public health emergency or a potential for a public health emergency is declared once viral samples become available.

.

The following would be considered new requirements

1. All rapid influenza detection devices commercially available would be required to meet the minimum performance standard stated in the regulation:

    a. Based on FDA's review of device performance (as stated in current labeling) of the 16 rapid antigen tests cleared for the market since 1998, all these devices meet the proposed minimum specificity criteria.
    b. However, seven manufacturers market tests that do not meet the proposed sensitivity criteria either for influenza A or for influenza B, or for both influenza types.
    c. Three of these seven manufacturers market new/improved tests that meet the proposed special controls.

2. All marketed devices will have to come into compliance with the new rule within one year of the final rule date. If the performance criteria are not met, the options would be to modify the product and submit a new 510k for FDA's review or withdraw the non-compliant product from the market.

3. Annual analytical reactivity testing with contemporary circulating influenza strains

    a. Manufacturers of RIDTs would have to develop a written plan (as part of their quality system) for annual testing of contemporary circulating strains.

    b. Failure to detect any of the provided/indicated strains in a panel would require a limitation in the labeling reflecting the absence of reactivity.

4. Testing of newly emergent strains

    a. All manufacturers of RIDTs will be required to test their device with any new influenza strain that is a subject of a declared public health emergency or potential for public health emergency by the Secretary of HHS.
    b. During a public health emergency, it is critical to effectively contain the spread of the virus in communities as well as in institutions, such as hospitals, retirement communities and nursing homes. In such a situation it is necessary to identify the most useful tools from among the available influenza diagnostics. Therefore, manufacturers should evaluate the analytical reactivity of their devices with the novel influenza virus as soon as samples become available.

5. Implementing design controls

    a. Although most IVD manufacturers already adhere to design controls, there may be some companies that do not. These manufacturers would have to incorporate design control practices into their quality system.

Summary

Despite the considerable resources invested in research and surveillance, influenza continues to be a public health challenge. Influenza virus infection is difficult to distinguish from other respiratory infections based on signs and symptoms alone, therefore reliable tests are critical to aid in an accurate diagnosis of influenza. Due to the public health implications of influenza virus infections and the wide use of RIDTs in US medical practice, FDA proposes to reclassify RIDTs currently regulated as Class I into Class II with Special Controls and to implement the requirement of Special Controls, along with Design Controls, to significantly improve the reliability of influenza tests over their Total Product Life Cycle. Improved and reliable influenza diagnostic devices would reduce the likelihood of false negative results, aid physicians in making accurate patient diagnosis and appropriate treatment decisions, and enable effective infection control and public health response during influenza outbreaks.

Questions for the Panel

1. Do you believe that General Controls are sufficient to provide a reasonable assurance of safety and effectiveness of the rapid influenza detection devices?

2. If you believe that General Controls are insufficient to provide reasonable assurance of the safety and effectiveness of the device, do you believe there is sufficient information to establish Special Controls to provide reasonable assurance of the safety and effectiveness of the device?

3. Do you agree that the proposed Special Controls are sufficient to mitigate the risks associated with rapid influenza detection devices?

4. Do you recommend that rapid influenza detection test systems currently regulated as Class I devices should be reclassified into Class II?

5. Do you agree that the Special Controls for the Respiratory Viral Panel regulation (21 CFR 866.3980) should be amended to add an annual monitoring requirement for any influenza device in a multiplex format?

Appendices

Appendix A

References

(2009). Performance of rapid influenza diagnostic tests during two school outbreaks of 2009 pandemic influenza A (H1N1) virus infection - Connecticut, 2009. MMWR. Morb. Mortal. Wkly. Rep. *58*, 1029-1032.

Biggs,C., Walsh,P., Overmyer,C.L., Gonzalez,D., Feola,M., Mordechai,E., Adelson,M.E., and Iacono,K.T. (2010). Performance of influenza rapid antigen testing in influenza in emergency department patients. Emerg. Med. J *27*, 5-7.

Cheng,C.K., Cowling,B.J., Chan,K.H., Fang,V.J., Seto,W.H., Yung,R., Uyeki,T.M., Houck,P.M., Peiris,J.S., and Leung,G.M. (2009). Factors affecting QuickVue Influenza A + B rapid test performance in the community setting. Diagn. Microbiol. Infect. Dis. *65*, 35-41.

Cruz,A.T., Demmler-Harrison,G.J., Caviness,A.C., Buffone,G.J., and Revell,P.A. (2010). Performance of a rapid influenza test in children during the H1N1 2009 influenza a outbreak. Pediatrics *125*, e645-e650.

Cunha,B.A., Thekkel,V., and Cohan,C. (2010). H1N1 influenza: contact investigation burden because of failure to institute influenza precautions in patients with negative rapid influenza diagnostic test results. Infect. Control Hosp. Epidemiol. *31*, 102-104.

Esposito,S., Daleno,C., Baldanti,F., Scala,A., Campanini,G., Taroni,F., Fossali,E., Pelucchi,C., and Principi,N. (2011). Viral shedding in children infected by pandemic A/H1N1/2009 influenza virus. Virol. J *8*, 349.

Ginocchio,C.C., Lotlikar,M., Falk,L., Arora,S., Kowerska,M., Bornfreund,M., and Manji,R. (2009a). Clinical performance of the 3M Rapid Detection Flu A+B Test compared to R-Mix culture, DFA and BinaxNOW Influenza A&B Test. J Clin. Virol. *45*, 146-149.

Ginocchio,C.C., Zhang,F., Manji,R., Arora,S., Bornfreund,M., Falk,L., Lotlikar,M., Kowerska,M., Becker,G., Korologos,D., de,G.M., and Crawford,J.M. (2009b). Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak. J Clin. Virol. *45*, 191-195.

Gordon,A., Videa,E., Saborio,S., Lopez,R., Kuan,G., Balmaseda,A., and Harris,E. (2010). Diagnostic accuracy of a rapid influenza test for pandemic influenza A H1N1. PLoS One *5*, e10364.

Gordon,A., Videa,E., Saborio,S., Lopez,R., Kuan,G., Reingold,A., Balmaseda,A., and Harris,E. (2009). Performance of an influenza rapid test in children in a primary healthcare setting in Nicaragua. PLoS One *4*, e7907.

Higgins,A.D., Shaw,C.J., Johnson,J.G., Navarro,A., Chapman,N.A., Ewers,S.D., Stockwell,J.W., Carpenter,J.M., Olivo,P.D., and Miao,L.Y. (2010). Monoclonal antibody kit for identification of the novel 2009 H1N1 influenza A virus. J Clin. Microbiol. *48*, 2677-2682.

Landry,M.L. (2011). Diagnostic tests for influenza infection. Curr. Opin. Pediatr *23*, 91-97.

Landry,M.L., Cohen,S., and Ferguson,D. (2008). Real-time PCR compared to Binax NOW and cytospin-immunofluorescence for detection of influenza in hospitalized patients. J Clin. Virol. *43*, 148-151.

Loeb,M., Singh,P.K., Fox,J., Russell,M.L., Pabbaraju,K., Zarra,D., Wong,S., Neupane,B., Singh,P., Webby,R., and Fonseca,K. (2012). Longitudinal study of influenza molecular viral shedding in Hutterite communities. J Infect. Dis. *206*, 1078-1084.

Louie,J.K., Guevara,H., Boston,E., Dahlke,M., Nevarez,M., Kong,T., Schechter,R., Glaser,C.A., and Schnurr,D.P. (2010). Rapid influenza antigen test for diagnosis of pandemic (H1N1) 2009. Emerg. Infect. Dis. *16*, 824-826.

Lu,P.X., Deng,Y.Y., Yang,G.L., Liu,W.L., Liu,Y.X., Huang,H., and Wang,Y.X. (2012). Relationship between respiratory viral load and lung lesion severity: a study in 24 cases of pandemic H1N1 2009 influenza A pneumonia. J Thorac. Dis. *4*, 377-383.

Mehlmann,M., Bonner,A.B., Williams,J.V., Dankbar,D.M., Moore,C.L., Kuchta,R.D., Podsiad,A.B., Tamerius,J.D., Dawson,E.D., and Rowlen,K.L. (2007). Comparison of the MChip to viral culture, reverse transcription-PCR, and the QuickVue influenza A+B test for rapid diagnosis of influenza. J Clin. Microbiol. *45*, 1234-1237.

Poehling,K.A., Zhu,Y., Tang,Y.W., and Edwards,K. (2006). Accuracy and impact of a point-of-care rapid influenza test in young children with respiratory illnesses. Arch. Pediatr. Adolesc. Med. *160*, 713-718.

Rahman,M., Vandermause,M.F., Kieke,B.A., and Belongia,E.A. (2008). Performance of Binax NOW Flu A and B and direct fluorescent assay in comparison with a composite of viral culture or reverse transcription polymerase chain reaction for detection of influenza infection during the 2006 to 2007 season. Diagn. Microbiol. Infect. Dis. *62*, 162-166.

Sambol,A.R., Abdalhamid,B., Lyden,E.R., Aden,T.A., Noel,R.K., and Hinrichs,S.H. (2010). Use of rapid influenza diagnostic tests under field conditions as a screening tool during an outbreak of the 2009 novel influenza virus: practical considerations. J Clin. Virol. *47*, 229-233.

Sandora,T.J., Smole,S.C., Lee,G.M., Chung,S., Williams,L., and McAdam,A.J. (2010). Test characteristics of commercial influenza assays for detecting pandemic influenza A (H1N1) in children. Pediatr. Infect. Dis. J *29*, 261-262.

Talbot,H.K., Williams,J.V., Zhu,Y., Poehling,K.A., Griffin,M.R., and Edwards,K.M. (2010). Failure of routine diagnostic methods to detect influenza in hospitalized older adults. Infect. Control Hosp. Epidemiol. *31*, 683-688.

Uyeki,T.M., Prasad,R., Vukotich,C., Stebbins,S., Rinaldo,C.R., Ferng,Y.H., Morse,S.S., Larson,E.L., Aiello,A.E., Davis,B., and Monto,A.S. (2009). Low sensitivity of rapid diagnostic test for influenza. Clin. Infect. Dis. *48*, e89-e92.

Vasoo,S., Stevens,J., and Singh,K. (2009). Rapid antigen tests for diagnosis of pandemic (Swine) influenza A/H1N1. Clin. Infect. Dis. *49*, 1090-1093.

Appendix B

Additional References

Chartrand,C., Leeflang,M.M., Minion,J., Brewer,T., and Pai,M. (2012). Accuracy of rapid influenza diagnostic tests: a meta-analysis. Ann. Intern. Med. *156*, 500-511.

Cheng,C.K., Cowling,B.J., Chan,K.H., Fang,V.J., Seto,W.H., Yung,R., Uyeki,T.M., Houck,P.M., Peiris,J.S., and Leung,G.M. (2009). Factors affecting QuickVue Influenza A + B rapid test performance in the community setting. Diagn. Microbiol. Infect. Dis. *65*, 35-41.

Cunha,B.A., Thekkel,V., and Cohan,C. (2010). H1N1 influenza: contact investigation burden because of failure to institute influenza precautions in patients with negative rapid influenza diagnostic test results. Infect. Control Hosp. Epidemiol. *31*, 102-104.

Ginocchio,C.C., Lotlikar,M., Falk,L., Arora,S., Kowerska,M., Bornfreund,M., and Manji,R. (2009a). Clinical performance of the 3M Rapid Detection Flu A+B Test compared to R-Mix culture, DFA and BinaxNOW Influenza A&B Test. J Clin. Virol. *45*, 146-149.

Ginocchio,C.C., Zhang,F., Manji,R., Arora,S., Bornfreund,M., Falk,L., Lotlikar,M., Kowerska,M., Becker,G., Korologos,D., de,G.M., and Crawford,J.M. (2009b). Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak. J Clin. Virol. *45*, 191-195.

Jernigan,D.B., Lindstrom,S.L., Johnson,J.R., Miller,J.D., Hoelscher,M., Humes,R., Shively,R., Brammer,L., Burke,S.A., Villanueva,J.M., Balish,A., Uyeki,T., Mustaquim,D., Bishop,A., Handsfield,J.H., Astles,R., Xu,X., Klimov,A.I., Cox,N.J., and Shaw,M.W. (2011). Detecting 2009 pandemic influenza A (H1N1) virus infection: availability of diagnostic testing led to rapid pandemic response. Clin. Infect. Dis. *52 Suppl 1*, S36-S43.

Sambol,A.R., Abdalhamid,B., Lyden,E.R., Aden,T.A., Noel,R.K., and Hinrichs,S.H. (2010). Use of rapid influenza diagnostic tests under field conditions as a screening tool during an outbreak of the 2009 novel influenza virus: practical considerations. J Clin. Virol. *47*, 229-233.

Appendix C

From FDA Website

1. Premarket Notification Process
2. Classification of Medical Devices
3. Medical Device Exemptions 510(k) and GMP Requirements
4. Reserved Medical Devices
5. Design Control Guidance For Medical Device Manufacturers
6. FDA Reclassification Process