Reclassification of Devices Detecting Influenza Viruses

FDA-Industry IVD Roundtable Meeting
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Outline

- Current Regulatory Status of Rapid Influenza Diagnostic Tests (RIDTs)
- FDA's Reclassification Proposed Rule
- Special Controls
  - Performance criteria and reference method
  - Annual reactivity and testing in a declared emergency
- Public Comments

Current Class I Influenza Diagnostics

§866.3330 Influenza virus serological reagents, Class I

Devices detecting viral antigens (RIDTs, DSFAs, DFAs)

- Rapid Influenza Diagnostic Tests (RIDT) intended for the detection of the influenza virus directly in clinical specimens exceed the limitations of the exemption and require a 510(k) submission

Devices detecting influenza nucleic acid are regulated as Class II:

- § 866.3980 Respiratory viral panel multiplex nucleic acid assay system
- § 866.3332 Reagents for detection of specific novel influenza A viruses, Class II

Reasons for Re-classification

- RIDTs are widely used in medical practice despite low sensitivity and failure to detect emerging influenza viruses
  - Sensitivity reported in the labeling of devices cleared since 1998:
    Flu A 73.8% (95% CI 64.4%-81.9%) - 94.2% (95% CI 91.0%-96.3%)
    Flu B 60.0% (95% CI 45.2%-73.6%) - 97.8% (95% CI 88.7%-99.6%)
  - Negative results frequently are not followed up as indicated in device labeling
  - Insufficient post-market monitoring to ensure that tests detect newly emerging influenza viruses
- FDA believes that general controls are insufficient to reasonably assure safety and effectiveness of RIDTs
- The special controls would mitigate the known risks associated with the use of Class I RIDTs and promote the development of improved diagnostics for influenza

Microbiology Devices Panel Meeting

- Microbiology Devices Panel meeting held June 13, 2013
  - Unanimously recommended reclassification of influenza virus antigen detection tests to Class II with special controls
- Proposed Order published May 22, 2014
- No plans for a second Panel Meeting
  - FDA is not aware of any significant changes in benefits or risks relating to the influenza virus antigen detection tests identified since the 2013 panel meeting
  - The reclassification process followed by FDA is in accordance with the applicable statutory provisions
  - FDA believes its interpretation of section 513(e), as amended by FDASIA, is reasonable and allows for reclassification of devices in the most efficient and effective manner

Public Comments

- Nine commenters expressed strong support for the proposed reclassification (AHL, AAP, ASM, SHEA)
  - …strongly supports the proposed rule to reclassify influenza virus antigen detection tests from class I to class II with special controls …
  - critical component in assuring acceptable RIDT performance is… to ensure the continued quality and performance of the assays
  - …FDA proposal to reclassify influenza virus antigen detection test systems from class I devices to class II devices… is… much needed and appropriately written
- Device manufacturers expressed concerns with the implementation of special controls

Proposed Special Controls

FDA proposed the following special controls (SC) to be included in the new regulation:

1. More appropriate minimum clinical performance criteria requirement
2. Use currently appropriate reference method for clinical studies
3. Requirement for annual reactivity testing
4. Provision for testing in a declared emergency or potential emergency once viral samples available

Minimum Performance Criteria & Reference Method

Specificity

All influenza detection devices should demonstrate specificity with a lower bound of the 95% CI > 90% for Flu A and Flu B

Sensitivity

When compared to viral culture as the reference method:

- Flu A - Point estimate of 90%; 95% CI lower bound 80%
- Flu B - Point estimate of 80%; 95% CI lower bound 70%

When compared to a molecular comparator method:

- Flu A - Point estimate of 80%; 95% CI lower bound 70%
- Flu B - Point estimate of 80%; 95% CI lower bound 70%

Comments - Reference Method

- Proposal to specify one reference method
  - Two minimum performance standards may encourage the use of a less accurate reference (culture) due to apparent higher sensitivity presented in labeling
- Strengths and weaknesses of the reference methods:
  - A lack of standardized culture methods among laboratories
  - Difficulty in finding a laboratory capable of performing viral culture procedures competently and accurately
  - Wide availability of FDA-cleared molecular methods among laboratories
  - A considerable body of knowledge accumulated by FDA about the performance of molecular assays in comparison to the viral culture
- FDA-cleared nucleic acid-based assays are an appropriate reference (molecular method)

Uniform Minimum Performance Criteria and a Single Reference Method

Specificity

All influenza detection devices should demonstrate specificity with a lower bound of the 95% CI > 90% for Flu A and Flu B

Sensitivity

When compared to a molecular comparator method:

- Flu A - Point estimate of 80%; 95% CI lower bound 70%
- Flu B - Point estimate of 80%; 95% CI lower bound 70%

Viral culture as a reference method (applicable only to tests marketed before the final rule):

- Flu A - Point estimate of 90%; 95% CI lower bound 80%
- Flu B - Point estimate of 80%; 95% CI lower bound 70%

Comments - Performance Criteria and Reference Method

- Selection of performance criteria

  (… was selected subjectively.. aimed at removing from market devices cleared prior to 2008)
- Process for notifying manufacturers that they do not meet new performance criteria
- Provisions for additional transition time
- Appeals mechanism

Reactivity Testing

Annual Reactivity Testing

Manufacturers of Class II influenza diagnostics targeting viral antigens or viral genes should develop a post-market test plan for annual reactivity testing with contemporary circulating viruses following a standardized protocol

Testing of Novel Viruses in a Declared Emergency

If a public health emergency or potential PH emergency for a novel influenza virus is declared, manufacturers must test reactivity of their assay with the novel virus as soon as samples become available

Absence of Reactivity (failure to meet acceptance criteria) will be reflected in labeling as a limitation

Comments - Reactivity Testing and Dissemination of Result

- Availability of a standardized panel of influenza viruses for annual testing
- Requirement to participate in the WHO PIP Network in order to access specimens
- Standardized protocol -
  - Will industry be engaged in development?
  - How will this protocol be developed and made available to manufacturers?
- Requirement to publicly disseminate reactivity test results

Availability of Influenza Viruses

- The CDC will provide a Human Influenza Virus panel to all influenza device manufacturers for the annual reactivity testing
- Requests will be accepted at http://www.cdc.gov/flu/fda-flu-panel/index.htm
- The panels will be distributed to allow adequate time for testing and publishing the results before the next flu season

Influenza Virus	Influenza strain designation	Quantity per vial	Number of vials
A(H1N1)	A/Brisbane/59/07	500µL	2
	A/Fujian Gulou/1896/2009	500µL	2
A(H3N2)	A/Perth/16/2009	500µL	2
	Texas/50/2012*	500µL	2
A (H1N1)pdm09	A/California/07/09*	500µL	2
	A/Washington/24/2012	500µL	2
B (Victoria lineage)	B/Brisbane/60/2008*	500µL	2
	B/Montana/5/2012	500µL	2
B (Yamagata lineage)	B/Wisconsin/01/2010	500µL	2
	B/Massachusetts/02/2012*	500µL	2

Participation in WHO PIP Network

- No requirement to participate in the WHO PIP Network to obtain CDC human influenza virus stocks due to specific and limited use of the viruses:

The CDC Human Influenza Virus Panel is intended to provide diagnostic test manufacturers with characterized influenza viruses to be used for internal evaluation testing for the purpose of generation of analytical performance data to be submitted to the FDA…

These materials are the property of the Centers for Disease Control and are made available on behalf of FDA. …materials may not be used for research activities or development of commercial products

- Select non-human virus stocks may require a PIP agreement

Standardized Testing Protocol

- Standardized testing protocol was developed in collaboration with the CDC
- The protocol will be included in the CDC Influenza Virus Panel Product Information Sheet
- Examples of steps included in the protocol:
  - For each stock virus, prepare a five-fold dilution series
  - Test each dilution in 5 replicates following the test procedure for a liquid sample, as stated in the manufacturer's Instructions for Use
  - Perform testing of all dilutions until there are no positive results at two consecutive dilution levels (0/5 replicates)
  - The last dilution producing positive results in at least one out of the five replicates tested is considered to be the minimum reactive concentration

A Certificate of Analysis

Information on passage history, propagation, and titer (EID_{50}/mL or $TCID_{50}$/mL)

CERTIFICATE OF ANALYSIS

INFLUENZA DIVISION
NCIRD/CCID
CENTERS FOR DISEASE CONTROL AND PREVENTION
1600 CLIFTON ROAD, MS: G16
ATLANTA, GA 30333 U.S.A.

PRECAUTIONS: INFECTIOUS SUBSTANCE. USE UNIVERSAL PRECAUTIONS

DESCRIPTION: Cleared allantoic fluid from chicken eggs containing infectious influenza virus

STRAIN DESIGNATION: A/PERTH/16/2009
CDC ID NUMBER: 2009719818
TYPE/SUBTYPE: INFLUENZA A/H3
DATE OF HARVEST (Lot #): 10/14/2009
PASSAGE HISTORY: E3/E3
PROPAGATION INFORMATION: 33.5◦C, 48 HOURS
QUANTITY/FORMAT: 0.5 ML OF MATERIAL IN A 2.0 ML SARSTEDT TUBE

STORAGE: -70º OR COLDER. THAW BY PLACING THE VIAL ON ICE FOR 15 MINUTES. KEEP AT 4°C UNTIL USE. USE WITHIN 4 HOURS OF THAWING. RE-FREEZING WILL RESULT IN LOSS OF INFECTIVITY AND MOLECULAR INTEGRITY.

QUALITY CONTROL*:

- **HA TITER = 128**
- **EID_{50} TITER/ML = $10^{8.2}$**
- **POSITIVE IDENTIFICATION BY HA GENE SEQUENCE CONFIRMED**
- **EXCLUSIVE TYPE/SUBTYPE DETECTION BY RT-PCR**
- **NO OBSERVED BACTERIAL OR FUNGAL CONTAMINATION**

*Description of QC testing methodology is provided on page 2 of this certificate

Approved by:

Supervisor

December 8th, 2009

Date

Reporting of Testing Results

- Results of the annual reactivity testing are expected to be publicly available by July 31 of each year
- Reactivity information should be added to the product PI (510(k) submission is not required)
- A special 510(k) is required to add a limitation if the device is not reactive
- In the case of a declared emergency, results should be posted 60 days after the samples become available
- Results presentation format included in the Panel Information Sheet

Influenza Virus (Type/Subtype)	Virus Strain Name	Starting Titer	Virus Serial Dilution Concentration (EID50/mL or TCID50/mL) and Number of Positive Results at Each Dilution								
		EID50 or TCID50	$2x10^{7.}_{4}$	$4x10^{6.}_{4}$	$8x10^{5.}_{4}$	$1.6x10^{5.4}$	$3.2x10^{4.4}$	$6.4x10^{3.4}$	$1.28x10^{2.4}$	$2.56x10^{7.}_{4}$	**$5.12x10^{2.8}$**
A(H1N1pdm)	**A/California/07/2009**	**$10^{8.}_{4}$**	**5/5**	**5/5**	**5/5**	**5/5**	**5/5**	**3/5**	**0/5**	**0/5**	**0/5**

Summary

Due to the public health implications of influenza virus infections and the wide use of RIDTs in US medical practice, FDA intends to reclassify rapid influenza diagnostic devices from Class I into Class II with special controls

- A uniform performance criteria and a single reference method are being considered
- Devices not meeting the minimum performance criteria should be removed from the market 12 months after publication of the final rule.
- A standardized panel of influenza viruses will be provided by CDC for the annual reactivity testing
- Testing results should be publicly available by July 31 of each year