

# Devices Detecting Influenza Viruses

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U.S. Food and Drug Administration  
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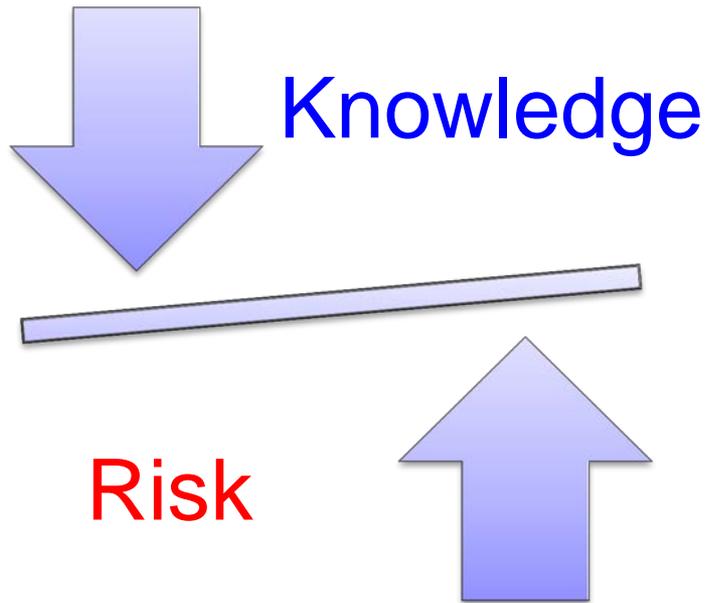


# Outline

- Background – Risk-based regulation of devices
- Current regulatory status of influenza diagnostic devices
- Why does FDA believe that current regulatory process for rapid influenza diagnostic tests (RIDTs) needs improvement?
- FDA's reclassification proposal
- Significance of the proposed approach

# Risk Based Regulation

Class I 510(k) exempt



Class III - PMA

Knowledge mitigates risk:

Class I - Low likelihood of harm

- **General Controls**

Class II - Moderate likelihood of harm

- Risk can be mitigated
- **General and Special Controls**

Class III - High or unknown likelihood of harm

- How to mitigate the risk is unknown
- **Pre-market Approval**

# Class I vs. Class II

## Class I

- Subject to general controls, e.g.
  - Registration and listing
  - Notifications of risks, repair, replacement, or refund
  - Adverse event reporting
- Generally exempt from 510(k) requirement unless exceed limitations of exemptions
- Subject to GMPs but generally exempt from design controls requirements

## Class II

- Subject to general and special controls, e.g.
  - Performance standards
  - Postmarket surveillance
  - Guidelines
- Subject to GMPs, including design controls
- Majority must submit premarket notification (510k) to FDA
- To be cleared, must demonstrate substantial equivalence



# Current Regulations of Influenza Diagnostics

## §866.3330 Influenza virus serological reagents, Class I

- Devices detecting antigens using specific labeled antibodies (RIDTs, DFAs, DSFAs)
- Can detect and often differentiate the presence of influenza A and B viruses

## § 866.3332 Reagents for detection of specific novel influenza A viruses, Class II

- Devices based on nucleic acid amplification principle
- Detect novel virus RNA in human respiratory specimens or viral cultures
- Special Controls: :
  - Guidance document which includes specific post-market monitoring
  - Limited distribution to laboratories with experienced personnel and biosafety equipment

## § 866.3980 Respiratory viral panel multiplex nucleic acid assay system, Class II

- Devices based on nucleic acid amplification principle
- Simultaneously detect multiple viruses in respiratory specimens or viral culture
- Influenza A and B, including Flu A subtypes, may be components of the panel
- Special control guidance documents addresses safety and effectiveness
  - Provide minimum performance criteria - sensitivity and specificity

# Current Class I Influenza Diagnostics

## §866.3330 Influenza virus serological reagents, Class I

Devices detecting antigens using specific labeled antibodies (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 510k submission
- Direct Specimen Fluorescence Antibody tests (DSFA) intended for the detection of the influenza virus **directly** in clinical specimens exceed the limitations of the exemption and require a 510k submission
- Direct Fluorescence Antibody tests (DFA) intended for the detection of the influenza virus from cultured viruses generally do NOT exceed the limitations of the exemption and do NOT require a 510k submission

# Rapid Influenza Diagnostic Tests

- RIDTs are widely used simple lateral flow immunoassays
- Detect viral proteins (antigens) using specific labeled antibodies
- Usually can detect and differentiate Flu A and B in respiratory specimens in less than 30 minutes
- Usually demonstrate high specificity, poor sensitivity
- Factors contributing to sub-optimal performance:
  - Quality and timing of the collected specimen
  - Genomic variations and newly emerging viruses
  - Proficiency of the operator
  - Quality/appropriateness of reagents

# What are the Issues?

## Low sensitivity and failure to detect emerging influenza viruses

- Sensitivity reported in the labeling for 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%)
- Tests not used as intended; negative results frequently not followed up by culture or molecular test as indicated in labeling
- Insufficient post-market monitoring to ensure that tests continue to detect newly emerging influenza virus strains
- Risk to Health
  - False negative results may lead to non-use/delay of antiviral therapy and failure to institute proper infection control procedures

# RIDT Performance in Labeling vs. Literature

TEST	510(k) STUDY Cell Culture Reference		LITERATURE		SENSITIVITY % (FLU A & FLU B)
	SEASON	SENSITIVITY % (FLU A & FLU B)	SEASON	REFERENCE METHOD	
A	2005-2006	79.3	2009	Culture	55.5
			2009	RT-PCR	45.0
B	2003-2005	85.2	2009	RT-PCR	46.7
C	1999	78.4	2008	RT-PCR	68.5
			2010	RT-PCR	64.1
	2005	73.4	2007-2008	Culture	28.7
D	2003	94.3	2009	RT-PCR	46.9
			2009-2010	Luminex xTAG	92.3
E	2006-2007	74.3	2009-2010	Luminex xTAG	100.0
F	2006-2007	79.5	2009	Culture and/or 2 RIDT	78.3
			2009	Culture, and/or RVP and/or 2 RIDT	41.2

Study where Sensitivity fell below LB 95%CI for A & B stated in labeling

# Why Use Rapid Influenza Diagnostic Tests?

- Simple, minimal, if any, equipment needed
- Can be used in low resource settings, remote rural areas, physician's offices, or outpatient clinics
- High positive predictive value and short time to results contributes to appropriate treatment decisions when the result is positive
- May be useful during influenza outbreaks in communities where public health labs are overwhelmed with clinical samples for nucleic acid based (RT-PCR) testing or culture

# Reasons for Re-classification

- FDA believes that general controls are insufficient to reasonably assure safety and effectiveness of RIDTs
- The addition of special controls would mitigate the known risks associated with the use of Class I RIDTs
- Establish and maintain more appropriate minimum performance criteria for influenza tests throughout their total product life cycle (TPLC)
- Promote the development and manufacturing of new and improved diagnostics for influenza that will meet the needs of patients, physicians, and public health

# FDA's Proposals

- Create a new Class II regulation for rapid influenza diagnostic devices currently regulated under 866.3330 as Class I
- Add special controls to the new regulation to:
  - Specify performance criteria that meet public health needs
  - Evaluate device performance against an appropriate current comparator method
  - Test reactivity with contemporary circulating viruses annually
  - In the event of a declared public health emergency or potential public health emergency, evaluate the ability of the device to detect the newly emergent influenza virus
- Design controls required for Class II devices would improve the reliability of RIDTs throughout the product life-cycle.
- Update Class II regulation 866.3980 (respiratory viral panel multiplex nucleic acid assay system) to include annual reactivity testing for devices detecting influenza viruses

# Scope of the Proposed Regulation

- Create a new Class II regulation for rapid influenza detection tests (RIDTs) with special controls
- The proposed reclassification regulation would apply to all RIDTs currently regulated under 21 CFR 866.3330
- If reclassified, all the currently marketed and new RIDTs based on immunoassay technology would be subject to the new regulation
- Fluorescent antibody influenza tests intended for use directly with clinical specimens (DSFAs) or with viral culture material (DFAs) will remain under the existing Class I regulation 21 CFR 866.3330

# Proposed Special Controls

FDA proposes the following special controls 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

# #1 Minimum Performance Criteria

## Specificity

All influenza detection devices should demonstrate specificity with a lower bound of the 95% CI exceeding 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%

## #2 Reference Method

- Clinical performance should be evaluated by comparison to the currently appropriate reference/comparator method
- Two methods are currently appropriate
  - Viral culture
  - FDA-cleared nucleic acid amplification based assays

# #3 Annual Reactivity Testing

Manufacturers of Class II influenza diagnostics targeting viral antigens or viral genes should develop a post-market test plan that includes:

- Annual reactivity testing with contemporary circulating viruses
  - Develop standardized protocols
  - Develop acceptance criteria
- Absence of reactivity will be reflected in labeling as a limitation

# Proposed Testing Protocol

- Obtain a standardized panel of current and recent circulating influenza viruses including the latest vaccine strains
- Selection of strains should be coordinated with FDA
- Each virus should be tested at clinically relevant concentrations ( $10^2 - 10^5$  TCID<sub>50</sub> /mL)
- Stocks should be serially diluted (three dilutions) to at least one dilution beyond the point of detection
- Each dilution should be tested in triplicate. To claim detection, device must be positive with all replicates at least at one dilution
- Viruses may be obtained from CDC or commercial vendors
- Testing may be conducted in-house or at a contract laboratory

# #4 Provision for Public Health Emergency

- Novel influenza viruses infecting humans may emerge, e.g. 2009 H1N1, H3N2v swine, and H7N9 avian influenza virus
- Due to potential for a public health emergency it is critical to know whether the existing influenza tests can effectively detect the new virus
- Rapid detection and characterization of novel influenza viruses are critical in order for CDC to assess the level of human to human transmission of the novel viruses
- If a public health emergency or potential public health emergency is declared by the Secretary of HHS involving a novel influenza virus, manufacturers must test reactivity of their assay with the novel influenza virus as soon as samples become available
- Failure to detect the indicated virus will result in a limitation in the labeling.

# Scope of Proposed Reclassification

If reclassified, all molecular and rapid influenza diagnostic tests will be subject to the following requirements:

- Minimum clinical performance criteria must be met by all FDA-cleared and future RIDTs
- Currently marketed devices not meeting performance criteria must be withdrawn from the market one year after the rule is finalized
- All device modifications will be subject to design controls
- Conduct annual testing of analytical reactivity with contemporary influenza strains
- Timely testing of newly emergent influenza viruses if a public health emergency or a potential for a public health emergency is declared
- If device is non-reactive with any of the tested viruses, labeling must be revised to reflect the limitation

# Significance of Reclassification

- Meeting sensitivity/specificity performance criteria
  - Seven (7) manufacturers market tests that would fail the proposed sensitivity criteria
  - Three (3) of these seven (7) manufacturers market new/improved tests that meet the proposed special controls
  - Options for meeting the requirements if performance criteria are not met:
    - withdraw the device from the market
    - modify the device and submit a new 510k within 1 year of the final rule
- Annual reactivity testing for all Class II influenza devices
- Testing of novel viruses when public health emergency or potential public health emergency is declared
  - Failure to detect the indicated viruses will result in a limitation in the labeling that reflects the absence of reactivity
- Implementation of design control practices

# Summary

Due to the public health implications of influenza virus infections and the wide use of RIDTs in US medical practice, FDA proposes:

- To reclassify rapid influenza detection devices from Class I into Class II with special controls
- To implement special controls, along with design controls to significantly improve the reliability of influenza tests over their TPLC and reduce the likelihood of false negative results

Improved and reliable influenza diagnostic devices would:

- Aid physicians to make accurate patient diagnosis and appropriate treatment decisions
- Allow for effective infection control during influenza outbreaks

# Q&A

