

MEETING THE STANDARDS:

FDA MANDATORY RAPID INFLUENZA DETECTION TEST (RIDTs) RECLASSIFICATION

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Learning Objectives

- Describe the FDA reclassification of rapid immunoassay detection tests (RIDT's) for 2018
- Discuss the reason for FDA's implementation of the new reclassification and how that impacts not only manufacturers but also the physician, the laboratory, and the patient
- Identify the information RIDT users must have from manufacturers to determine whether or not their current testing meets the reclassification

TOPICS COVERED

- How does FDA evaluate *in- vitro* diagnostic devices (IVDs)?
- What does FDA mean by “reclassification” of an IVD test?
- Why did FDA “reclassify” rapid, influenza diagnostic tests (RIDTs)?
- Why have some rapid influenza tests become unsafe and ineffective over time?
- What are the implications of “reclassification” of RIDTs for manufacturers, distributors, physicians and clinical laboratories and POC facilities?
- Why is there continued value in use of rapid RIDT’s for influenza detection and diagnosis of infection?

FDA's Overall Mission



Ensure that diagnostic devices/systems on the market are “safe and effective”

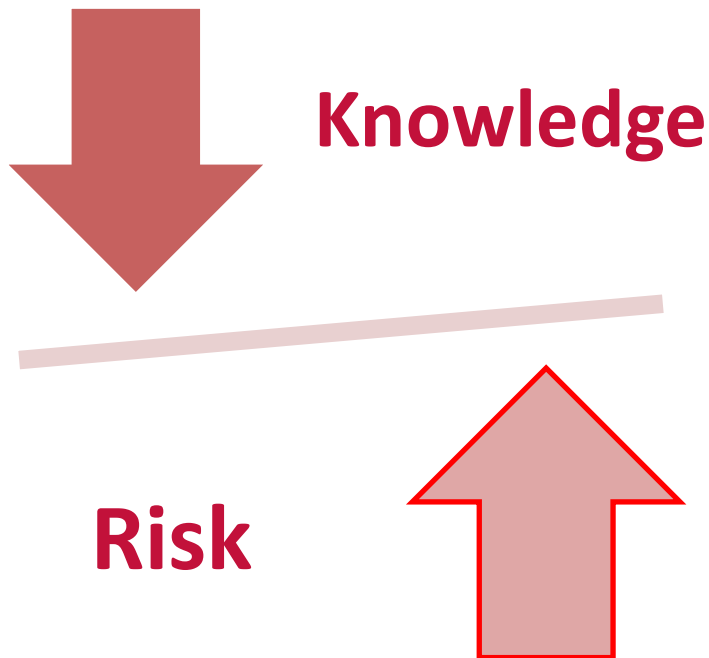
Get “safe and effective” diagnostic devices/systems to market as quickly as possible

Reasons to Regulate *in-vitro* Diagnostics (IVDs)

- To ensure that IVDs are “safe and effective” for
 - their intended use
 - by an intended user
 - in their intended location
- A “safe and effective” IVD should give a correct answer consistently which can be understood by all intended users which may include....
 - highly trained laboratory professionals
 - minimally trained healthcare workers

FDA's Risk Class Based Regulation of IVDs

“Knowledge Mitigates Risk”



Class I - Low likelihood of harm

Class II - Moderate likelihood of harm

Class III - High or unknown likelihood of harm
Significant risk

Scope of FDA Reclassification Rule

Rapid Influenza Diagnostic Tests (RIDTs)

Intended Use = detect influenza virus antigens directly from clinical specimens, previously FDA classified as “*influenza virus serological reagents*”; now-

- ❖ Reclassified from 21 CFR 866.3330, Class I to 21 CFR 866.3328, Class II with Special Controls

Devices in this category are visual and reader based RIDTs.

Note: Molecular rapid influenza tests are already FDA categorized as Class II devices

Why did FDA decide to Change the Classification of Influenza RIDT's?

Let's take a closer look at the public health consequences of influenza infections and the influenza virus itself that causes an infection, for the answer

Public Health Need for Accurate & Rapid Influenza RIDT's

Clinical Decisions:

Testing decisions = linked directly to clinical decisions related to antiviral treatment and clinical management of individual patients

Surveillance:

Control of suspected outbreaks: Decisions by CDC to initiate prevention /control measures for acute respiratory disease outbreaks of suspected influenza

Public Health Consequences of Influenza Infections in the U.S.

-**Typical Season:** 9-36 million infections, ~200,000 hospitalizations, and 12-50,000 deaths

-**Annual Economic Burden:** \$52 to \$199 billion in healthcare costs, lost productivity

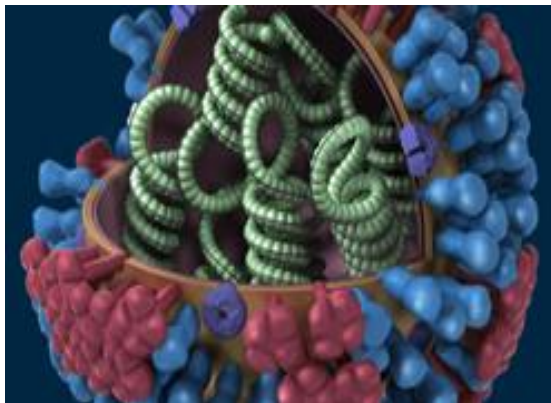
Individual Risk Factors: Seasonal variation associated with **Antigenic drift of circulating viruses**; human host factors i.e. environmental, demographic, genetic, and clinical

-**Emergence of novel viruses** with high human-to-human transmissibility and virulence causes epidemics and pandemics (e.g. **2009-2010 Influenza A H1N1**)

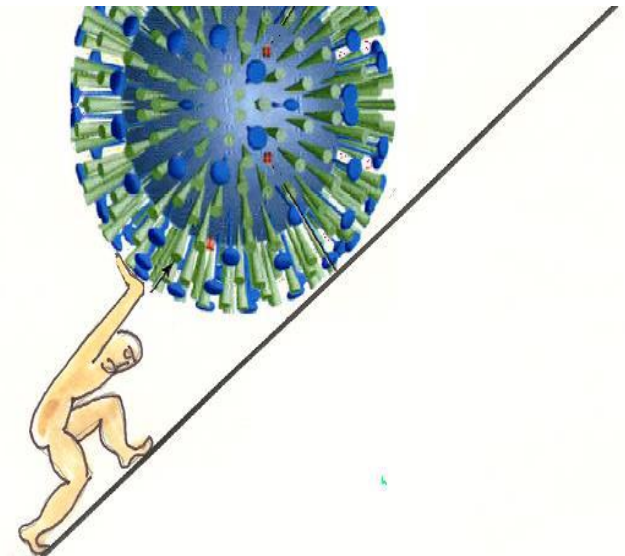
Influenza Viruses and the Seasonality of Influenza Infections

Q. Why do we need revaccination against influenza every year with a different cocktail of influenza virus antigens?

A. Because influenza viruses mutate continuously and rapidly, changing their surface antigenic glycoproteins (HA and NA) genes

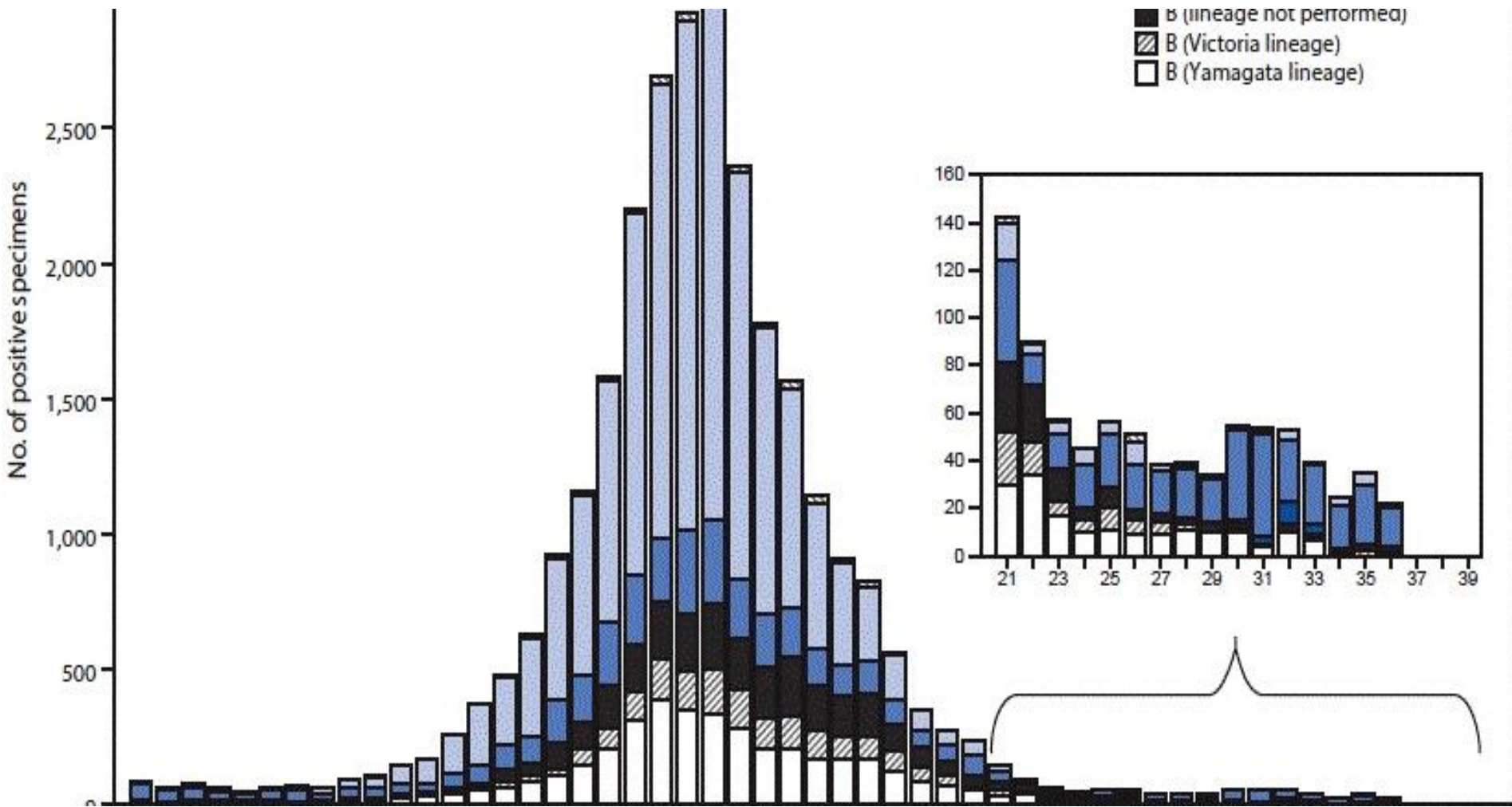


Influenza virus surface proteins hemagglutinin (HA) & neuraminidase (NA).
<https://www.cdc.gov/flu/images.htm>



CDC Oct. 2015-Sept. 2016 = 76,293 Cases

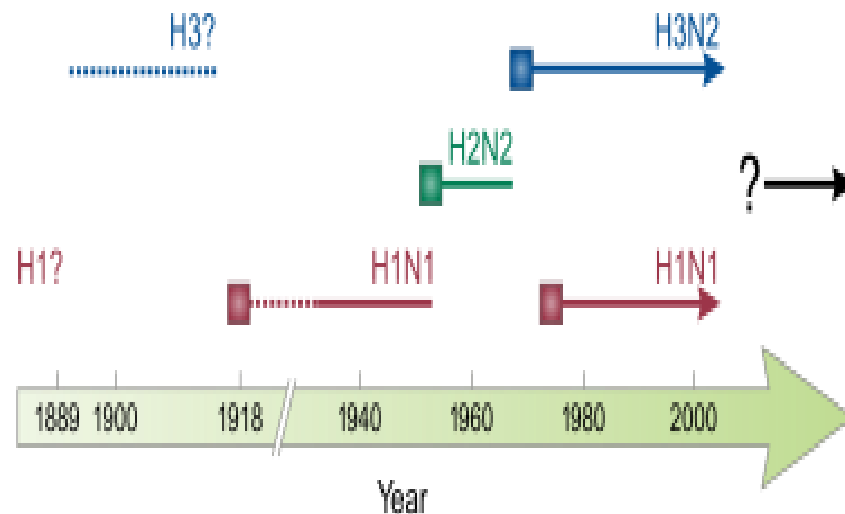
Virus Strains Circulating=Influenza AH1N1 / AH3N2 / +B's



New Antigenic Drifts with Pandemic Potential

- **CDC/WHO** have concerns when a new subtype of A with a novel HA or NA emerges in a human host from an animal population = five **H7N9** Chinese epidemics since 2013, each more pathogenic

Influenza A virus subtypes in the human population



Reasons for Sub-optimal Performance of Influenza RIDT's

- Antigenic drift / newly emerging viruses = changed surface protein antigens . Current RIDTs may not now have the specific antibodies to recognize them
- Quality and timing of the collected specimen after infection . 48h samples = highest viral load
- Competency of the operator to perform the test
- Quality of reagent manufacturing

What Type of Problems with RIDT's were Identified by FDA?

Low Sensitivity and Failure to detect Influenza Viral Infection in devices FDA cleared since 1998:

Flu A Point Estimate Ranges =

Sensitivity: 73.8% (95% CI: 64.4%-81.9%)

Specificity: 94.2% (95% CI: 91.0%-96.3%)

Flu B Point Estimate Ranges =

Sensitivity: 60.0% (95% CI: 45.2%-73.6%)

Specificity: 97.8% (95% CI: 88.7%-99.6%)

- Lack of post-market monitoring to ensure tests continue to detect newly emerging influenza virus strains

Clinical Decisions

Inadequate Performance as a Risk to Public Health

- **False negative results:** may lead to overuse of antibiotics and failure to institute proper infection control procedures
- **False positive results:** may lead to unnecessary use of anti-viral therapy or infection controls and may delay antibiotic treatment needed for a bacterial infection

Summary of FDA's Reclassification of Influenza RIDTs

- Scope of Reclassification
- Reasons for Reclassification
- Special Controls
- Implementation Date
- Implications of RIDT Reclassification for Manufacturers and Distributors; Physicians and Laboratory Facilities

Class I vs. Class II Requirements

Class I = current classification of RIDTs

Subject to General Controls e.g.

- Registration and Listing
- Notifications of risks, repair, replacement, or refund
- Adverse event reporting

Subject to GMP's, including Design Controls

Must submit a 510(k) to FDA for a new device

Class II = reclassification of RIDTs

Subject to General Controls

Subject to Special Controls

Subject to GMPs, including Design Controls

Must submit a 510(k) to FDA for a new device

Summary of FDA's Reasons for Reclassification of RIDTs

- Influenza diagnostics currently regulated as Class I, do not all meet the needs of patients, physicians, or public health
- Need to mitigate known risks associated with poor performance of Class I RIDTs due to viral antigenic changes
- FDA believes General Controls are insufficient to reasonably assure “safety and effectiveness” of RIDTs
- Re-classification to Class II will allow for Special Controls to be applied to RIDTs
- Will establish and maintain minimum performance criteria for RIDT’s throughout their product life cycle
- Promote the development of new and improved RIDTs

Implementation of Special Controls for Class II RIDTs: Impact on Manufacturers

1. Minimum clinical performance criteria requirement demonstrated using a currently appropriate and FDA accepted comparator method.

2. Requirement for annual reactivity testing and results reporting

3. Provision for testing in a declared emergency or potential emergency once viral samples are available

1. Minimum Clinical Performance Criteria & Reference/Comparator 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 = 90%; 95% CI lower bound 80%
- Flu B Point Estimate = 80%; 95% CI lower bound 70%

When compared to a molecular comparator method:

- Flu A Point Estimate = 80%; 95% CI lower bound 70%
- Flu B Point Estimate = 80%; 95% CI lower bound 70%

2. Annual Reactivity Testing and Result Reporting

Manufacturers of Class II RIDTs should develop a post-market test plan for **annual reactivity testing** with contemporary circulating viruses following a standardized protocol. This will enable comparability between RIDTs

- These viruses will be available each year from CDC
- 3.** Also any new emerging influenza strain will be available if a public health emergency is declared
- Testing protocol and proposed results interpretation and presentation format will be included with the viral panels

CDC Analytical Panel for Mandatory Annual Testing by Manufacturers

Human Influenza Virus Panel for the 2017 annual reactivity testing may be requested from CDC at the following website

<https://www.cdc.gov/flu/dxfluviruspanel/index.htm>

The 2017 Panel:

Influenza Virus	Updated
A(H1N1)	A/Brisbane/59/2007
	A/Fujian Gulou/1896/2009
A(H3N2)	A/Perth/16/2009
	A/Hong Kong/4801/2014*
A (H1N1)pdm09	A/California/07/2009*
	A/Michigan/45/2015*
B (Victoria lineage)	B/Brisbane/60/2008*
	B/Texas/2/2013
B (Yamagata lineage)	B/Wisconsin/01/2010
	B/Phuket/3073/2013*

New Labeling Requirements for Influenza RIDTs

Testing results from the last 3 years since a device was cleared must be added to the labeling in a separate section or provided on the manufacturer's website by July 31 of each year

In the absence of reactivity, a manufacturer would need to include a limitation in the test labeling regarding reactivity with the specific strain(s) not detected by the test

These labeling updates do not need to be submitted to FDA

What Remains Unchanged for Manufacturers?

- Compliance with GMP regulations
- 510k submission to FDA for all new RIDTs, whether antigen or molecular, manual or reader result-based
- The requirement for all RIDTs to conduct clinical and analytical performance studies
- A CLIA waiver submission is required if intended use is POC
- Manufacturer's responsibility to ensure reliable performance throughout the device's "Total Product Life Cycle"

Implementation Date of the Reclassification

- Final Order effective date: February 13, 2017
- **Special Controls compliance date for devices legally marketed prior to February 13, 2017 is **January 12, 2018****
- Reclassification letter info. for manufacturers if need to submit or resubmit an RIDT
 - Regulation: 21 CFR 866.3328, Influenza virus antigen detection test system
 - Regulatory Class: Class II
 - Product Code: PSZ

Reclassification Implications for Distributors of RIDTs

- After January 12, 2018, FDA could take actions, pursuing seizure of Influenza RIDTs held by a distributor that do not meet the Special Controls
- Although a low FDA priority ,distributors should manage their inventory so that they only possess and distribute devices that meet the Special Controls as of the compliance date

RIDT Reclassification: Implications for Physicians and Laboratory Facilities

- Some currently manufactured and distributed influenza antigen RIDTs **will not achieve the new Special Controls performance criteria** and will be withdrawn from the market on January 12th, 2018
- **Physicians and testing facilities who still possess Influenza antigen RIDTs that do not meet the Special Controls by January 12th can continue to use them until they expire**
- **When purchasing new influenza RIDTs**, physicians and laboratories should check test labeling claims and manufacturer's websites to see if the manufacturer has conformed with reclassification Special Controls

Why Continue to Use Influenza Antigen RIDTs?

All antigen–based RIDTs that conform to the new FDA Special Controls reclassification requirements will continue to be valuable tools for diagnosing influenza because :

Reasons to Continue Using Influenza Antigen RIDTs

- Low cost ,and minimum if any equipment needed
- Can be used in low resource settings, remote rural areas, physicians offices or outpatient clinics
- Have high positive predictive value, improved sensitivity, short time to results contributing to appropriate treatment decisions, e.g. reducing use of antibiotics and timely administration of anti-virals
- Useful during influenza outbreaks when public health labs are overwhelmed with samples for nucleic acid (RT-PCR) testing or culture

FDA Contact for Any Additional Questions

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Questions?