Reclassification of Influenza Virus Antigen Detection Test Systems Intended for Use Directly with Clinical Specimens
21 CFR 866

BACKGROUND
In May of 2014, the Food and Drug Administration (FDA) released a proposed order to reclassify antigen based rapid influenza diagnostic tests (RIDTs) and solicited comments from stakeholders through a docket and a public meeting. The Association of Public Health Laboratories (APHL) was involved in providing feedback to FDA during this time. The final order was published in the Federal Register (82 FR 3609) on January 12, 2017.

SHORT SUMMARY
In the final order, effective February 13, 2017, FDA reclassifies antigen based RIDTs intended to detect influenza virus directly from clinical specimens that are currently regulated as influenza virus serological reagents from class I to class II with special controls and into a new device classification regulation.

MAJOR CHANGES
- Antigen based RIDTs are reclassified from class I to class II with special controls to help improve overall quality of testing for influenza by establishing new minimum performance criteria
- Premarket notification will be required for RIDTs to assist in providing reasonable assurance of safety and effectiveness
- Special controls requirements:1
  1. Sensitivity and specificity, or positive and negative percent agreement for each claimed specimen type in the intended use, must meet one of the following minimum clinical performance criteria:2
     a. For influenza A or B devices evaluated by comparison to an FDA-cleared nucleic acid based test or other FDA accepted comparator method other than viral culture:
        • The positive percent agreement estimate must be at least 80% with a lower bound of the 95% confidence interval (CI) that is ≥ 70%
        • The negative percent agreement estimate must be at least 95% with a lower bound of the 95% CI that is ≥ 90%
     b. For devices evaluated by comparison to viral culture
        • Influenza A:
           o The sensitivity estimate must be at least 90% with a lower bound of the 95% CI that is ≥ 80%
        • Influenza B:

1 Information in this section is often pulled verbatim from the final order
2 A currently appropriate and FDA accepted comparator method must be used to establish assay performance in clinical studies

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The sensitivity estimate must be at least 80% with a lower bound of the 95% CI that is ≥ 70%

- Influenza A and B
  - The specificity estimate must be at least 95% with a lower bound of the 95% CI that is ≥ 90%

2. Devices must have annual analytical reactivity testing performed with contemporary influenza strains and must meet the following criteria:
   a. The appropriate strains will be identified by FDA in consultation with the Centers for Disease Control and Prevention (CDC). In absence of strain availability from CDC, FDA will find an alternative source
   b. FDA will determine a standardized protocol to test the strains
   c. By July 31 of each calendar year, the result of the last three years of annual analytical reactivity must be included as part of the device’s labeling. Devices that have not been on the market for three years will need to include all years of analytical reactivity data since the device received marketing authorization from FDA.

3. In the event that a Secretary declares a public health emergency that involves an influenza virus strain:
   a. Within 30 days from the date FDA notifies manufacturers that characterized viral samples are available for test evaluation, manufacturers must have testing performed on the device according to a standardized protocol determined by FDA.
   b. Within 60 days from the date FDA notifies manufacturers that characterized viral samples are available for test evaluation and continuing 3 years from that date, the results of the influenza emergency analytical reactivity testing must be included as part of the device’s labeling in a tabular format.

- Implementation
  1. For antigen based RIDTs that have been legally marketed prior to the effective date of February 13, 2017, FDA does not intend to enforce compliance until January 12, 2018. After this date, if manufacturers do not comply with special controls, FDA will consider taking action under its usual enforcement policies.
  2. For antigen based RIDTs that have not been legally marketed prior to February 13, 2017, or devices that have been legally marketed but are required to obtain a 510(k) clearance due to a modification or significant change, manufacturers will need to obtain 510(k) clearance to come into compliance with the final order before marketing their device. If the device is marketed after February 13, 2017 without obtaining 510(k) clearance, FDA will consider taking action under its usual enforcement policies.

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