

Guidance for Industry and FDA Staff

In Vitro Diagnostic Devices to Detect Influenza A Viruses: Labeling and Regulatory Path

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Preface

Public Comment

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Table of Contents

I. INTRODUCTION.....	4
II. BACKGROUND	5
III. THE LEAST BURDENSOME APPROACH.....	5
IV. SCOPE	6
V. LABELING INFORMATION.....	6
A. Label recommendations	7
B. Labeling recommendations	7
VI. PREMARKET PATHWAYS FOR NEW OR MODIFIED PRODUCTS INTENDED TO DETECT INFLUENZA A VIRUSES, INCLUDING A NOVEL INFLUENZA A VIRUS, OR TO DETECT AND DIFFERENTIATE A SPECIFIC INFLUENZA A VIRUS.....	11

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

FDA is issuing this guidance to inform industry and agency staff of recommended steps to ensure the safe and effective use of in vitro diagnostic (IVD) devices intended for use in the detection of influenza A (or A/B) viruses directly from human specimens. FDA is taking this action because of recent significant public health concerns associated with emergence of an avian influenza A virus strain as a human pathogen in Southeast Asia.

This guidance document addresses recommendations for fulfilling labeling requirements applicable to all IVDs intended to generally detect influenza A (or A/B) virus directly from human specimens, with a particular emphasis on ensuring appropriate labeling for legally marketed influenza A (or A/B) test devices whose clearances are not based on data addressing performance with regard to novel influenza A viruses¹ infecting humans (e.g., H5N1, H9N2, H7N7). [Such devices have been classified under 21 CFR 866.3330.] This guidance also outlines the premarket regulatory path for new or modified devices intended to generally detect influenza A viruses, or intended to detect and differentiate a specific novel

¹ Novel influenza A viruses are new or re-emergent human strains of influenza A that cause cases or clusters of human disease, as opposed to those human strains commonly circulating that cause seasonal influenza and to which human populations have residual or limited immunity (either by vaccination or previous infection).

influenza A virus infecting humans.² It also includes broad recommendations regarding information for assessing the clinical performance and utility of all such devices.

II. Background

Several subtypes of influenza A circulate among birds and other animals. They all have the ability to cause epidemics of varying intensity and severity by drift or shift of antigenic types resulting in minor to profound effects on antigenicity and pathogenicity. During the past several decades there have been primarily two influenza A virus subtypes (H3N2 and H1N1) infecting humans worldwide. The spread of the influenza A H5N1 virus within bird species, along with sporadic transmission to humans, has heightened awareness of the potential for a novel influenza A virus to cause a pandemic in humans.

All of the influenza A (or A/B) devices cleared by FDA before the issuance of this guidance and classified under 21 CFR 866.3330 are designed to generally detect influenza A viruses in human respiratory specimens (e.g., washes, aspirates, and swabs). Theoretically, these devices would react with any hemagglutinin (HA) or neuraminidase (NA) subtype, since they are usually designed to target nucleoprotein antigen(s) common to all influenza A viruses, rather than antigen(s) unique to the two surface glycoproteins HA and NA of any one particular influenza A subtype. None of these devices is designed, or intended, to detect a specific influenza A virus, or to detect and differentiate one specific influenza A virus from another (e.g., H5N1 from H3N2).

Sensitivity of any of these devices to detect influenza A virus depends on biological and pathophysiological factors associated with both the virus and its human host. These include clinical course of disease, replication rate of the virus, viral tissue tropism, and susceptibility of the human host. When disease is caused by a novel subtype (e.g., H7N7 or H5N1), these factors may differ from seasonal circulating strains of influenza, possibly affecting device performance. Particularly when a novel influenza A virus is emerging, optimal specimens, or timing of specimen collection, for detecting that virus may not be known. For devices cleared on the basis of performance characteristics established when only influenza A/H3 and A/H1 viruses were circulating, there is no evidence that the devices would reliably detect novel influenza A viruses from human respiratory samples. Also, these testing devices are not intended to detect and differentiate a specific human-infecting novel influenza A virus.

III. The Least Burdensome Approach

In developing this guidance, we carefully considered the relevant statutory criteria for Agency decision-making. Also, we considered the burden that may be incurred in the attempt to follow the statutory and regulatory criteria. We believe that we have considered the least burdensome approach to resolving the issues presented in this guidance document.

² Devices that are intended to specifically detect a novel influenza A virus are classified into class II under 21 CFR 866.3332, Reagents for detection of specific novel influenza A viruses. Additional guidance for these devices is found in "Class II Special Controls Guidance Document: Reagents for Detection of Specific Novel Influenza A Viruses," which contains recommendations for the contents of premarket notification submissions, labeling, and postmarket data collection and analysis.

If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the document, "A Suggested Approach to Resolving Least Burdensome Issues." It is available on our Center web page at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>.

IV. Scope

This guidance addresses labeling for in vitro diagnostic devices that are intended to generally detect influenza A (or A/B) viruses directly from patient specimens. These devices have been classified under 21 CFR 866.3330, and currently include microscopic immunofluorescence tests, enzyme immunoassays for influenza A viral antigens, and rapid influenza tests including those that are CLIA-waived. The guidance also addresses premarket pathways for devices classified under this regulation as well as for devices that are intended to detect a specific novel influenza A virus and are classified under 21 CFR 866.3332.³

V. Labeling Information

IVD devices for detection of influenza A (or A/B) viruses directly from human specimens, like other devices, are subject to statutory requirements that their labeling not be false or misleading in any particular. Their labeling may be rendered misleading by the omission of information that is material to the representations made in the labeling or that is material with respect to the labeled or usual conditions of use. (Federal Food, Drug and Cosmetic Act (the Act), Sections 502(a), 201(n); 21 USC §§ 352(a), 321(n)). IVD devices for detection of influenza must also provide adequate directions for use and adequate warnings and precautions. (Section 502(f); 21 USC § 352(f)). Specific labeling requirements for IVD devices are set forth in 21 CFR 809.10. This guidance sets forth recommendations for labeling IVD devices intended for use to generally detect influenza A viruses directly from human specimens, to help assure that they continue to comply with these legal requirements. Providing objective and clear labeling information to laboratorians and clinicians is particularly important to ensure safe and effective use of these devices when novel influenza A viruses are emerging.

FDA recognizes that labeling for influenza A (or A/B) IVDs that generally detect these viruses and were cleared prior to the issuance of this guidance under 21 CFR 866.3330 may not reflect information that may be material to use of these IVDs in light of the emergence of novel influenza A viruses. FDA recommends that manufacturers make any revisions to printed labeling necessary to comply with the underlying statutory and regulatory requirements for labeling, in light of these current circumstances within six months of the issuance of this guidance, and encourages manufacturers to implement labeling changes as soon as possible to help assure that the information is available to users.

³ Additional guidance for devices classified under 21 CFR 866.3332 is found in "Class II special Controls Guidance Document: Reagents for Detection of Specific Novel Influenza A Viruses."

To ensure compliance with section 502 of the Act and 21 C.F.R. 809.10, FDA recommends that labels and labeling for IVD devices intended for use in detection of influenza A (or A/B) generally, as an aid in the diagnosis of influenza, address the items identified below.⁴ Depending on the specific technological characteristics of your product, some of these recommendations may not apply.

A. Label recommendations

Information required to appear on the label of IVDs is set forth in 21 CFR 809.10(a). Among these requirements, IVD labels must contain a statement of the intended use of the product.⁵ The statement of intended use of each IVD intended to generally detect influenza A or A/B directly from human specimens that was cleared for marketing prior to the issuance of this guidance may have included a statement regarding the need to confirm negative test results. FDA recommends that on the label, the statement of intended use for influenza IVDs intended to generally detect influenza A be clarified by a statement such as "Negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other management decisions."

For devices previously cleared, we recommend that manufacturers make this change in the statement of intended use without submitting a new 510(k). See 21 CFR 807.81(a)(3)(ii) (requiring new 510(k) only for a major change in intended use).

B. Labeling recommendations

Requirements for the labeling for IVDs are found in 21 CFR 809.10(b). These requirements are commonly fulfilled through the package insert. The following recommendations address specific portions of the required labeling.

1. Intended use

IVD labeling must contain a statement of the intended use of the product.⁶ A specific statement of intended use is included in labeling of all cleared 510(k)s, and influenza devices cleared prior to the issuance of this guidance under 21 CFR 866.3330, may have included a statement regarding the need to confirm negative test results. As with the IVD label, FDA recommends that the statement of intended use in the labeling for IVDs intended to generally

⁴ The Act defines "label" as "a display of written, printed or graphic matter upon the immediate container of any article" and specifies that a requirement "that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper." (Section 201(k), 21 USC 321(k).) The Act defines "labeling" as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." (Section 201(m); 201 USC 321(m).) The IVD labeling regulation in 21 CFR 809.10 follows this distinction and specifies some requirements for the label, while other requirements apply to labeling generally. This guidance document makes recommendations in relation to the regulatory provisions.

⁵ 21 CFR 809.10(a)(2).

⁶ 21 CFR 809.10(b)(2).

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detect influenza A (or A/B) be clarified by a statement such as “Negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other management decisions.”

For devices already cleared, we recommend that manufacturers make this change in the statement of intended use without submitting a new 510(k). See 21 CFR 807.87(a)(3)(ii) (requiring new 510(k) only for a major change in intended use).

In addition, we recommend that statements such as the following be included after the intended use statement of your package insert:

- “Performance characteristics for influenza A were established when influenza A/H3 and A/H1 were the predominant influenza A viruses in circulation. When other influenza A viruses are emerging, performance characteristics may vary.”
- “If infection with a novel influenza A virus is suspected based on current clinical and epidemiological screening criteria recommended by public health authorities, specimens should be collected with appropriate infection control precautions for novel virulent influenza viruses and sent to state or local health departments for testing. Viral culture should not be attempted in these cases unless a BSL 3+ facility is available to receive and culture specimens.”

2. Summary and Explanation

The Summary and Explanation section of your product insert⁷ should be factual and refrain from a discussion of a particular novel influenza A virus (e.g., influenza A/H5N1) as a cause of pandemic human infection. A discussion about a specific novel influenza A virus when you have shown that your device can analytically detect, for example, A/H5 virus(es) may mislead the user to think that the analytical detection described (elsewhere in the package insert for your device) applies to the clinical detection of influenza A/H5N1 virus. However, for influenza IVDs cleared under 21 CFR 866.3330, prior to the issuance of this guidance, performance characteristics for the detection of influenza A/H5N1 virus, or any other specific novel influenza A virus, from human specimens have not been established. Such a discussion may also mislead users to believe that a novel influenza virus is present whenever the result is positive, when in fact, the device is not intended to identify or differentiate specific novel influenza A viruses.

3. Reagents and Materials

In the section on Reagents and Materials,⁸ we recommend, if applicable, that you state the master influenza virus strain used to develop the monoclonal or polyclonal antibodies incorporated into your device, and the specifications for control materials, including level of virus, source of that virus, method of inactivation and method for determining non-infectiousness.

⁷ 21 CFR 809.10(b)(3).

⁸ 21 CFR 809.10(b)(5)(i).

4. Precautions

In the Precautions section,⁹ we recommend that you specify procedures for handling, storing, and disposing of specimens, including a reiteration and expansion of the procedures for working with specimens suspected to be infected with a novel influenza strain. (See recommendations for cautions in Section V.B.1 of this document.)

5. Specimen Collection

Under Specimen Collection,¹⁰ we recommend that you state that inadequate or inappropriate specimen collection, storage, and transport are likely to yield false negative test results. We also recommend that you state that training in specimen collection is highly recommended because of the importance of specimen quality.

6. Results

We recommend that you incorporate into the Results section¹¹ directions for reporting results that include statements such as the following:

- "Report negative test results as Influenza A (or B) virus antigen not detected. This result does not exclude influenza viral infection."
- "Report positive test results as 'Positive for influenza A (or B) virus antigen. This result does not rule out co-infections with other pathogens or identify any specific influenza A virus subtype.'"

7. Limitations

We recommend providing statements such as the following under Limitations¹²:

- If your device detects both influenza A and B viruses, without distinguishing the two, a statement such as "additional testing is required to differentiate influenza type A and B viruses."
- If your device detects influenza A and distinguishes it from influenza B viruses, a statement such as "Additional testing is required to differentiate any specific influenza A subtypes or strains, in consultation with state or local public health departments."

⁹ 21 CFR 809.10(b)(5)(ii).

¹⁰ 21 CFR 809.10(b)(7).

¹¹ 21 CFR 809.10(b)(9).

¹² 21 CFR 809.10(b)(10).

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- "Children tend to shed virus more abundantly and for longer periods of time than adults. Therefore, testing specimens from adults will have lower sensitivity than testing specimens from children."
- "Positive and negative predictive values are highly dependent on prevalence. False negative test results are more likely during peak activity when prevalence of disease is high. False positive test results are more likely during periods of low influenza activity when prevalence is moderate to low."
- "Individuals who received nasally administered influenza A vaccine may have positive test results for up to three days after vaccination."
- "If your test uses monoclonal antibodies, a statement such as "Monoclonal antibodies may fail to detect, or detect with less sensitivity, influenza A viruses that have undergone minor amino acid changes in the target epitope region."
- "If positive or negative interference has been reported for any commonly used collection materials or substances that may be endogenously or exogenously introduced into a specimen prior to testing, you should advise users of the possibility of false negative or false positive results due to such interference."

8. Performance Characteristics

We recommend that the Performance Characteristics section¹³ describe the population(s) (i.e., geographical location, specimen types, and age groups) used to establish the performance characteristics of the device and provide the influenza season (calendar years) when this evaluation took place, along with the predominant influenza subtype(s) observed during that time.

We recommend that you stratify positive and negative test results from your submitted clinical study by specimen source(s) and age. We also recommend that you separate results for children <5 years of age, older children, and adults. If this information is not available, you should add a Warning statement such as "Differences in performance are expected when this test is used on specimens from adults versus from children, but specific differences are not known."

In addition, for influenza A virus detection devices, analytical sensitivity levels (limits of detection) are commonly described in this section. This information is based on testing dilutions of one or more cultured influenza A strains and has not been done in a consistent manner from manufacturer-to-manufacturer. If you have a narrative or table that indicates your device may detect various influenza A virus subtypes, we recommend removing this section from your labeling, unless you have used a standardized viral quantitation method (e.g., WHO Manual on Animal Influenza Diagnosis and Surveillance, Virus titration procedure) and followed the approach recommended in CLSI-EP 17A (Protocols for

¹³ 21 CFR 809.10(b)(12).

Determination of Limits of Detection and Limits of Quantitation; Approved Guideline), or its updated version.

If you represent results of these standardized quantitation methods for various influenza A virus subtypes in the labeling, we also recommend qualifying the information with a statement such as “Performance characteristics for detecting influenza A virus from human specimens when these or other influenza A virus subtypes are emerging as human pathogens have not been established.” Such a statement may help avoid misleading users into thinking that this analytical information on the detection of specific influenza A viruses applies to detection of these specific influenza A viruses in human clinical specimens.

VI. Premarket pathways for new or modified products intended to detect influenza A viruses, including a novel influenza A virus, or to detect and differentiate a specific influenza A virus

FDA recognizes the clinical and public health need for devices capable of reliably detecting influenza A generally, as well as the need for devices to detect and differentiate a specific clinically significant novel influenza A virus from other influenza A viruses. (Note: Please see the definition of novel influenza A virus in the footnote on p. 4).

Two device classifications currently exist for influenza tests. Devices intended to generally detect influenza A (or A & B) viruses have been classified into class I, under 21 CFR 866.3330. More recently, through evaluation of an automatic class III designation under section 513(f)(2) of the Act, FDA classified reagents for detection of specific novel influenza A viruses into class II, under 21 CFR 866.3332. Manufacturers seeking to market tests for influenza may seek to establish substantial equivalence to predicate devices already classified under these regulations, depending on the intended use of their new devices. (This does not guarantee that any particular test will be able to establish substantial equivalence to devices already classified under either of these two regulations.)¹⁴

FDA recommends that manufacturers seeking to market tests intended for the detection of a specific novel influenza virus directly from human specimens seek to establish substantial equivalence to a predicate device classified under 21 CFR 866.3332. FDA recommends that manufacturers seeking to market tests for detecting influenza A generally, seek to establish substantial equivalence to a predicate device already classified under 21 CFR 866.3330. This includes manufacturers who seek to market tests intended to detect influenza A generally, but who wish to establish performance that includes performance where novel influenza A

¹⁴ In addition, if a new influenza test device is found to be substantially equivalent for its labeled uses but there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling, and that use could cause harm, in accordance with section 513(i)(1)(E) of the Act, 21 USC 360c(i)(1)(E), the substantial equivalence determination letter will specify appropriate limitations to be included in the labeling for the device. See also Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff, December 3, 2002. Available at: <http://www.fda.gov/cdrh/ode/guidance/857.html>

viruses are in circulation in addition to seasonal circulating strains. (If such performance was established and the device was cleared with this information included in its intended use, labeling recommendations of this guidance intended to avoid misleading users about the known performance of the device would not apply.)

Although devices within the classification described in 21 CFR 866.3330 are Class I devices, which are generally exempt from premarket notification, under FDA regulations, a premarket notification must be submitted and the new test found to be substantially equivalent to a legally marketed predicate device before an influenza test device intended to detect an influenza A virus infecting humans directly from human specimens may be legally marketed.¹⁵ Specifically:

- An IVD for detection of influenza is not exempt from 510(k) to the extent that it meets limitations on exemption defined in 21 CFR 866.9.
 - Under 21 CFR 866.9(c)(6), an IVD that is intended for use in identifying or inferring the identity of a microorganism directly from clinical material is not exempt from premarket notification requirements.
 - In addition, an IVD to detect influenza may trigger the limitations in 21 CFR 866.9(a) (if it differs in intended use from existing legally marketed devices classified under 21 CFR 866.3330) or 21 CFR 866.9(b) (if it operates using a different fundamental scientific technology from existing influenza tests in that classification).

In addition, for devices already cleared for marketing under 21 CFR 866.3330, FDA recommends that manufacturers submit a new 510(k) before making claims that the device can detect influenza A viruses including any novel influenza A virus.¹⁶ See 21 CFR 807.81(a)(3)(ii) (requiring new 510(k) for major changes in intended use).

Because of differences between novel influenza A viruses and seasonal ones with respect to such factors as clinical course of disease, replication rate of the virus, viral tissue tropism, and susceptibility of the human host, we anticipate that overall performance of a test intended for detection of influenza generally where novel influenza A viruses are in circulation may differ from performance of the cleared test. This may necessitate changes in the directions for use and interpretation, all of which could significantly affect the safety or effectiveness of the device. Consequently, these require evaluation to determine whether the device remains substantially equivalent to other legally marketed devices within that classification (i.e., 21 CFR 866.3330).

¹⁵ If, after evaluating the 510(k), FDA concludes that the new device is not substantially equivalent to the legally marketed class I predicate, the new influenza test will be a class III device unless subsequently reclassified into class I or II. See Section 513(f)(1), 21 U.S.C. 360c(f)(1).

¹⁶ If you propose to change your intended use to indicate that the device can detect and differentiate specific novel influenza A viruses, rather than continuing to provide information only on the presence of influenza A generally, we recommend that you attempt to establish equivalence to a device classified under 21 CFR 866.3332.

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If a new influenza test is not found to be substantially equivalent to an existing device under either 21 CFR 866.3330 or 866.3332, it will be automatically classified into class III in accordance with section 513(f)(1) of the Act. However, an applicant may petition FDA in accordance with section 513(f)(2) of the Act to make a "de novo" risk-based classification of a device that is not substantially equivalent to a predicate device. This path may be especially appropriate for a new device that detects several influenza A viruses, generally or specifically, and also differentiates a specific novel influenza A virus from other influenza A viruses, if that product is found not substantially equivalent to any existing influenza test device. This path may also be appropriate for a new device that detects novel influenza virus and is intended for near-patient testing (point-of-care).

Performance characteristics for generally detecting influenza A virus should be established by comparing the device test results to culture performed under standardized conditions, or other acceptable methods, using the device in the same manner that it will be used during clinical practice, and using specimens obtained from patients with an influenza-like illness. Thus, the performance should be described in relation to the influenza A subtype(s) infecting humans during the influenza season in which the evaluations are conducted.

To provide FDA with a basis to assess the performance of a device that detects a specific novel influenza A virus (subtype or strain), we recommend that you submit data from clinical evaluations with fresh specimens from patients with influenza caused by the novel influenza A virus and other commonly circulating influenza viruses, along with specimens from patients with influenza-like illness not due to influenza viruses. Fresh samples are preferred for obtaining these data. However, archived samples may be useful to expand representation of specimens (e.g., geographically diverse, different specimen types recommended). Archived samples may be useful to provide the variety of specimen types from patients who have other respiratory infections, and from whom fresh specimens may not be readily available.

The appropriate regulatory pathway to gather information/data to support a finding of substantial equivalence for any of these influenza diagnostic devices, and at the same time make them available for use during a time of medical need, is the investigational device exemption (IDE) available under section 520(g) of the Act and regulations at 21 CFR part 812. Specific requirements that may apply to the investigation of a novel influenza A test device will depend upon the risk associated with the manner in which the study is conducted, i.e., whether the diagnosis will be confirmed by another, medically established diagnostic product or procedure, circumstances by which the results will be reported to the patient's physician, and the clinical implications of this information. Depending on how the study is conducted, you may need to submit an IDE application to FDA for approval before initiating the investigation. For information on how to submit an IDE, see *Guidance on IDE Policies and Procedures*, issued on January 20, 1998; available at <http://www.fda.gov/cdrh/ode/idepolicy.html>. For questions on IDE submissions please contact the IDE Staff at 301-594-1190.