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Draft – Not for Implementation

Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564

Draft Guidance for Laboratory Manufacturers and Food and Drug Administration Staff

DRAFT GUIDANCE

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For questions about this document, contact the CDRH Guidance Program in the Office of Policy at CDRH-Guidance@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

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Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564

Draft Guidance for Laboratory Manufacturers and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from threats such as emerging infectious diseases, exposures to harmful chemicals, and public health emergencies (PHEs). FDA is issuing this guidance to describe the Agency's enforcement policy for certain laboratory manufacturers offering certain unauthorized in vitro diagnostic devices (IVDs) for immediate response to chemical, biological, radiological, or nuclear (CBRN) agents in the absence of a declaration applicable to IVDs under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (hereafter referred to as an "applicable 564 declaration").

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

The Emergency Use Authorization (EUA) authority under section 564 of the FD&C Act allows FDA to help strengthen the nation's public health protections against CBRN threats by facilitating the availability and use of medical countermeasures (MCMs) needed during an actual or potential emergency or material threat. Under section 564 of the FD&C Act, when the Secretary of Health and Human Services declares that the circumstances exist justifying the issuance of EUAs, FDA may authorize certain unapproved medical products or unapproved uses of approved medical products to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN agents when certain criteria are met, including that there are no adequate, approved, and available alternatives. FDA has used this authority to authorize emergency use of IVDs for eight infectious diseases that have emerged over the past years: H1N1 (2009), H7N9 (2013), MERS-CoV (2013), Ebola (2014), Enterovirus D68 (2015), Zika (2016), Coronavirus Disease 2019 (COVID-19) (2020), and mpox (formerly monkeypox) (2022).[1]

In the context of emergent situations involving CBRN threats, there may be a public health need for certain IVDs to be available for immediate response purposes. An emergent situation is, for purposes of this guidance, the period of time between detection of the exposure or outbreak and, either, resolution of the exposure or outbreak or issuance of an applicable 564 declaration. In this time period, the exposure or outbreak may start out small or be confined to a particular geographic area. Some exposures or outbreaks may be resolved without ever reaching a level for which a declaration is made, while others may continue to grow, eventually leading to an applicable 564 declaration. In the past, during this period of time, laboratory manufacturers offered laboratory developed tests (LDTs) for which FDA has had a general enforcement discretion approach. However, as discussed in the preamble to the final rule amending FDA regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory ("LDT Final Rule"),[2] FDA is phasing out this general enforcement discretion approach for LDTs. Accordingly, FDA is issuing this guidance with our enforcement policy for "immediate response" tests.

Prior to an emergent situation and after an emergent situation has been resolved, when there might not be a critical need for a coordinated and immediate public health response and where the implications of false results may not have as serious implications for public health decision-making, such tests may fall within the enforcement discretion policies described in section V.B of the preamble to the LDT Final Rule. FDA intends to consult with CDC regarding a potential emergent situation based on relevant facts and circumstances, including information about the localized or broad nature of the exposure or outbreak, method(s) and ease of transmissibility, analyses of transmission potential, population at risk, morbidity and mortality rates,

[1] The year in each parentheses represents when the first EUA for an IVD was issued for each outbreak.

[2] Medical Devices: Laboratory Developed Tests, final rule (May 6, 2024). In the preamble to the LDT Final Rule, FDA included several enforcement discretion policies but noted that the enforcement discretion policies discussed in section V.B do not apply to certain tests needed for immediate response to an emergent situation. However, in the absence of an emergent situation, certain LDTs may fall within an enforcement discretion policy discussed in section V.B of the preamble to the LDT Final Rule.

hospitalization and other healthcare utilization rates, availability of existing medical countermeasures, and any information received from test manufacturers and other clinical laboratories.[3] Based on this consultation with CDC, when appropriate, FDA intends to broadly announce that the enforcement policies described in section V.B of the preamble to the LDT Final Rule do not apply due to the emergent situation and the public health benefits of the considerations described in this guidance.

III. Scope

This policy applies only to "immediate response" tests, which are tests:

- intended to detect or diagnose a serious or life-threatening disease or condition that may be attributed to a newly identified, previously unknown, or unusual CBRN agent or agents; or a known agent or agents that result in a newly identified or unusual clinical presentation of such a disease or condition;
- needed for immediate response in an emergent situation to a potential case or cases of such disease or condition for which there is no adequate, approved/cleared/authorized, and available alternative to the test for detecting or diagnosing such disease or condition; and
- intended to help ensure the government's coordinated and effective public health response during an emergent situation.

This policy does not apply to tests with home specimen collection or at home tests.[4]

IV. Policy

FDA does not intend to object to the offering of "immediate response" tests when:

- the test is manufactured and offered by laboratory manufacturers described in Section A;
- the test has been appropriately validated as described in Section B;
- FDA is notified as described in Section C;
- appropriate transparency is provided as described in Section D;
- the test is labeled for prescription use only; and
- there is no applicable 564 declaration.[5]

[3] Given the critical need for an immediate public health response in the circumstances in which the policy described in this guidance applies, FDA does not intend to object to the offering of "immediate response" tests, consistent with the factors listed in section IV below, prior to such consultation.

[4] Different risks are presented with specimen collection in the home versus the healthcare setting. For example, home collection raises issues such as whether the lay user can safely and properly collect the specimen, whether the components of the specimen transport media are safe for use in the home environment (since some may be toxic), proper shipment, and adequate stability of the specimen given the time lapse between collection and testing and the potential impact of shipping conditions (such as if the specimen sits in a hot truck). Tests that are also interpreted in the home may involve a lay user collecting their specimen, running the test, and interpreting and reporting their results accurately.

[5] We note that this draft guidance relates to the time period *prior to* the exposure or outbreak resolving or resulting in an applicable 564 declaration, whereas FDA has issued another draft guidance that describes proposed factors FDA would plan to assess in deciding whether to issue an enforcement policy regarding IVDs *during* a declared

When an applicable 564 declaration is made, FDA does not intend to object to the continued offering of an immediate response test as described in this policy while the laboratory manufacturer prepares and submits an EUA request to FDA and while FDA reviews the EUA request where the laboratory manufacturer submits the EUA request within a reasonable period of time. FDA believes 21 days from the date of the declaration is generally a reasonable period of time to prepare and submit an EUA request for such tests given that they have already been validated.

Based on historical timelines, FDA expects that an exposure or outbreak generally will either resolve or an applicable 564 declaration will be made within 12 months[6] of the start of an emergent situation. If no applicable 564 declaration is made within this approximate timeframe, FDA anticipates that the public health rationale for the enforcement policy described in this guidance will no longer apply at that time. FDA would therefore expect the laboratory manufacturer to cease offering the immediate response test or seek approval/clearance/authorization for the test. FDA does not intend to object to the continued offering of an immediate response test as described in this policy while the laboratory manufacturer prepares and submits a premarket submission to FDA and while FDA reviews the premarket submission, where the laboratory manufacturer submits the premarket submission within a reasonable period of time from the date of the first offering of the immediate response test.[7] Generally, FDA believes a reasonable period of time from the date of the first offering of the immediate response test to the date of the premarket submission would be around 12 months. FDA will be available to discuss specific circumstances regarding the test and emergent situations with the laboratory manufacturer and encourages laboratory manufacturers to reach out to discuss any issues, including if more time is needed to prepare a submission.

If FDA identifies a significant problem or concern with an immediate response test offered as described in this policy, FDA intends to notify the laboratory manufacturer and work with the laboratory manufacturer to address the concerns as appropriate. If the concerns cannot be adequately addressed in a timely manner, FDA generally would expect the laboratory manufacturer to take appropriate steps, which could include that the laboratory manufacturer stop offering the test, conduct a recall of the test, and/or notify end users by issuing corrected test reports indicating prior test results may not be accurate. If at any point FDA denies or declines authorization of an EUA request or other marketing submission, FDA would expect the laboratory manufacturer to stop offering the test.

This policy addresses only premarket review requirements and does not address other requirements such as medical device reporting (MDR) under 21 CFR Part 803. Part 803

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emergency under section 564. See FDA draft guidance document "Consideration of Enforcement Policies During a Section 564 Declared Emergency" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-enforcement-policies-tests-during-section-564-declared-emergency

[6] The typical timeframe for HHS to make an applicable 564 declaration after the initial emergence of an exposure or outbreak is within twelve months, albeit it has been shorter more recently. For example, it was about one month for COVID-19 and about two months for mpox between outbreak emergence and an applicable 564 declaration.

[7] Until FDA has phased out the general enforcement discretion approach regarding premarket review requirements (stages 4 and 5 of the phaseout policy as discussed in the LDT Final Rule), FDA generally is not expecting compliance with premarket review requirements for IVDs offered as LDTs.

establishes the requirements for medical device reporting for manufacturers, among others (21 CFR 803.1(a)), including a requirement that manufacturers submit a timely report to FDA if they become aware of information that reasonably suggests that their test may have caused or contributed to a death or serious injury, or has malfunctioned and this test or a similar test that they market would be likely to cause or contribute to a death or serious injury if the malfunction were to recur (21 CFR 803.50(a)).

Regardless of this policy, FDA retains discretion to pursue enforcement action against the offering of unauthorized IVDs at any time with respect to violations of the FD&C Act, Public Health Service Act, or FDA regulations, and intends to do so when appropriate for protection of the public health.

A. Test Manufacturers

This policy applies to immediate response tests that are:

- designed, manufactured, and used within a single laboratory that is certified under the Clinical Laboratory Improvement Amendments (CLIA)[8] and meets the requirements to perform high complexity testing, has demonstrated the ability to develop a similar diagnostic test consistent with FDA regulatory requirements[9], is an entity with which FDA has not communicated any current compliance concerns, and where such laboratory is a:
    - United States Government (USG) laboratory,
    - State or local public health laboratory,
    - laboratory operating under an agreement (formal or informal) with the USG; or
- designed, manufactured, and distributed by the Centers for Disease Control and Prevention (CDC) for use by CLIA-certified laboratories that meet the requirements to perform high complexity testing, where such laboratories are:
    - within CDC,
    - within CDC's Laboratory Response Network (LRN), or
    - under an agreement with CDC.

B. Test Validation

The test should be appropriately validated on the test systems (including instruments and reagents) intended for clinical use. For example, for a PCR-based test for an infectious disease, FDA generally recommends that the following validation studies be completed prior to testing and that summary validation and performance information be made publicly available:

[8] Such laboratories may include those operating under State licensure programs that have exemption from CLIA program requirements, and USG laboratories implementing their laboratory programs under agreements with CMS, including the Department of Defense and the Veterans Health Administration.

[9] For example, a laboratory manufacturer may demonstrate its ability to develop a similar test in compliance with FDA regulatory requirements through an FDA-cleared, approved, or authorized test with the same underlying technology, such as polymerase chain reaction (PCR) or mass spectrometry.

- clinical evaluation of at least 30 positive and 30 negative clinical samples; or if not available, (synthetic[10]) contrived specimens using unique negative patient samples,
- limit of detection (analytical sensitivity),
- inclusivity (analytical reactivity), and
- cross-reactivity (analytical specificity).

FDA is available to laboratory manufacturers who would like to discuss their approach for validation in specific circumstances.

Where the need for an immediate response test can be anticipated, FDA encourages pre-EUA submissions[11] for preliminary review of available validation information.

Laboratory manufacturers offering tests as described in this policy should concurrently perform additional validation studies as appropriate, which could help prepare for, among other things, an EUA request in the event there is an applicable 564 declaration. For example, the clinical evaluation should be repeated with natural clinical specimens when it becomes feasible to do so. If it is not feasible to complete an evaluation with natural clinical specimens prior to requesting an EUA, FDA may require such a study as a condition of authorization.

C. Notification to FDA of Test Offering

Prior to or concurrent with initiation of testing, a notification should be sent by email to CDRH-EUA-Templates@fda.hhs.gov with a subject line "Notification of Immediate Response Test." FDA recommends the following information be included with the notification, as applicable:

- the serious or life-threatening disease or condition that the test is intended to detect or diagnose and rationale for use of the test under existing circumstances,
- contact individual's name, address, phone number, and email address,
- general laboratory information including the name and address of the laboratory manufacturer, the name of the laboratory director, and the CLIA ID number,
- general test information including the test name, test methodology (including specimen type), the date testing begins, and the estimated testing capacity,
- a statement describing the laboratory manufacturer's regulatory and compliance standing (e.g., any warning letters recently received, etc.),
- a list of other similar tests developed by the laboratory manufacturer that have approval, clearance, or authorization, and
- a link to where summary information on the test will be publicly available.

[10] When synthetic material is used, it should closely mimic the natural pathogen or CBRN agent. For example, if the pathogen is an RNA virus, synthetic material should be full length or long strand RNA and not short fragments of RNA or DNA.

[11] For more information about pre-EUA submissions, see section III.C. of the FDA Guidance document entitled "Emergency Use Authorization of Medical Products and Related Authorities" available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities

When a laboratory manufacturer stops offering a test previously offered as described in this policy, notification should be sent to FDA by email to CDRH-EUA-Templates@fda.hhs.gov with a subject line "Discontinuation of Immediate Response Test Offering."

D. Transparency

In order to provide transparency, when the test is offered as described in this policy, test reports and test ordering information provided by laboratory manufacturers should prominently disclose that the test was manufactured for use as a part of an immediate public health response during an emergent situation to detect or diagnose the disease or condition that may be attributed to a CBRN agent (which disease or condition should be identified), and has not been reviewed or authorized by FDA. Unless a test is authorized by FDA, any statements in the test reports and other labeling that expressly state or imply that the test has been reviewed or authorized by FDA would be false or misleading. Similarly, any statements in the test reports and other labeling that state or imply that FDA authorization is imminent or pending could be false or misleading. A test shall be deemed to be misbranded if its labeling is false or misleading in any particular.[12]

Since tests offered as described in this policy will not have been reviewed or authorized by FDA, laboratory manufacturers should make summary validation and performance information publicly available. If a laboratory manufacturer believes that the posting of such information would present a risk to national security or would otherwise be inappropriate, the laboratory manufacturer should contact FDA to discuss.

Laboratories must immediately notify appropriate Federal, State, or local public health agencies of test results, to the extent required by applicable laws.

[12] See section 502(a)(1) of the FD&C Act, 21 U.S.C. 352(a)(1).