Enforcement Policies for Certain In Vitro Diagnostic Devices - Draft Guidances
June 5, 2024

Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello and thanks for joining us for today's CDRH Webinar. This is CDR Kim Piermatteo of the United States Public Health Service and I serve as the Education Program Administrator in the Division of Industry and Consumer Education, in CDRH's Office of Communication and Education. I'll be your moderator for today's webinar.

We are holding this webinar to provide an overview of two draft guidances which were issued on May 6, 2024. The first draft guidance is titled, Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564, and the second draft guidance is titled, Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency.

Today, we will review the scope and key elements of each draft guidance as applicable to in vitro diagnostic devices or IVDs and provide responses to previously submitted questions.

Before we begin, I'd like to provide two administrative reminders. First, please make sure you've joined us through the Zoom app, and not through a web browser to avoid technical issues. And second, the intended audience for this webinar is industry. Trade press reporters are encouraged to consult with the CDRH Trade Press Team at cdrhtradepress@fda.hhs.gov. And members of national media may consult with FDA's Office of Media Affairs at FDAOMA@fda.hhs.gov.

I'd now like to introduce today's presenter, Toby Lowe, Acting Deputy Director for the Office of Health Technology number seven for in vitro diagnostic devices within the Office of Product Evaluation and Quality within CDRH.

We'll begin with a presentation from Toby and then address previously emailed questions about today's topic. Thank you all again for joining us, I'll now turn it over to Toby.

Toby Lowe: Thanks, Kim. Good afternoon, everyone, and thanks for joining us today. We'll start off by providing a bit of background and then discuss the two draft guidance documents.

The FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, exposure to harmful chemicals, and public health emergencies. Appropriately safe and effective diagnostic tests are critical to the diagnosis, treatment, tracking, and interruption of transmission of infectious diseases during outbreaks, as well as for diagnosing and treating diseases or conditions caused by chemical, biological, radiological, and nuclear threat agents, referred to as CBRN threat agents.

During an outbreak or exposure caused by a CBRN threat agent, the HHS Secretary may issue what we refer to as a 564 declaration. This refers to section 564 of the Federal Food, Drug, and Cosmetic Act, the FD&C Act, which gives the Secretary authority to declare that circumstances exist justifying the issuance of Emergency Use Authorizations, EUAs. FDA may then 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.

FDA has used its authority to authorize emergency use of in vitro diagnostics, IVDs, for eight infectious diseases that have emerged over the past 15 years: H1N1 in 2009, H7N9 in 2013, MERS-CoV in 2013, Ebola in 2014, Enterovirus D68 in 2015, Zika in 2016, COVID-19 in 2020, and mpox in 2022. After all previous declarations under section 564, FDA has generally expected laboratory developed tests, LDTs, to comply with applicable requirements and has issued EUAs for LDTs for many of these situations.

Some exposures or outbreaks may be resolved without ever reaching a level for which a 564 declaration is made, while others may continue to grow, eventually leading to an applicable 564 declaration. In the past, during this period of time without an applicable 564 declaration, laboratory manufacturers offered LDTs for which FDA has had a general enforcement discretion approach. However, as discussed in the preamble to the LDT Final Rule, FDA is phasing out this general enforcement discretion approach for LDTs.

FDA has issued two draft guidance documents discussing the use of enforcement policies, which we may also refer to as enforcement discretion policies, for IVDs to help support future public health responses. The first of these draft guidances is the Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564. During this webinar, we will generally refer to this guidance as the Immediate Response Test Policy or the Immediate Response guidance.

The second draft guidance is titled Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency. During this webinar, we will generally refer to this guidance as the Consideration of Enforcement Policies During 564 guidance or the Considerations guidance.

We'll first dive into the specifics of the Immediate Response Test Policy draft guidance. When finalized, this draft guidance will describe the FDA's enforcement policy for certain laboratory manufacturers offering certain unauthorized IVDs for immediate response to CBRN agents in the absence of a declaration applicable to IVDs under section 564 of the FD&C Act.

As mentioned earlier, historically, during this time period without an applicable 564 declaration, laboratory manufacturers offered LDTs for which FDA had a general enforcement discretion approach that the FDA is now phasing out.

For purposes of this guidance, FDA defines this period of time between detection of the exposure or outbreak and resolution of the exposure or outbreak, or issuance of an applicable 564 declaration, as an Emergent Situation. This draft guidance applies during an emergent situation, when there may be a public health need for certain IVDs to be available for immediate response purposes.

Based on 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 an emergent situation and the public health benefits of the considerations described in the guidance.

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.

As described in this draft policy, during an emergent situation, FDA does not intend to object to the offering of immediate response tests when the test is manufactured and offered by certain laboratory manufacturers; the test has been appropriately validated; FDA is notified prior to or concurrent with initiation of testing; appropriate transparency is provided, such as, summary validation and performance information being made publicly available; the test is labeled for prescription use only; and there is no applicable 564 declaration. Importantly, this draft policy addresses only premarket review requirements.

The draft policy would apply only to immediate response tests, which are tests that are: 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 to 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. The policy would not apply to tests with home specimen collection or at home tests.

The draft policy would apply to two types of laboratory manufacturers. First, the policy would apply to immediate response tests when a single laboratory designs, manufacturers, and uses the test, where such laboratory manufacturer is a United States Government, USG, laboratory, state or local public health laboratory, or a laboratory operating under an agreement with the USG. Such an agreement may be formal or informal.

Additionally, the laboratory manufacturer should have demonstrated the ability to develop a similar diagnostic test consistent with FDA regulatory requirements and be an entity with which FDA has not communicated any current compliance concerns.

Second, this policy would also apply to immediate response tests designed, manufactured, and distributed by CDC for use by laboratories that are within CDC, within CDC's Laboratory Response Network, LRN, or under an agreement with CDC. In all cases, under CLIA, the laboratories using immediate response tests must be certified and meet the requirements to perform high complexity testing.

The draft guidance describes additional mitigations for immediate response tests offered under this policy, including, first, the laboratory manufacturer should appropriately validate the test system intended for clinical use. For example, for a PCR-based test for an infectious disease, generally FDA recommends that certain validation studies be completed prior to testing and that summary validation and performance information be made publicly available. The recommended studies for this type of test are limit of detection, inclusivity, cross-reactivity, and clinical evaluation of at least 30 positive and 30 negative clinical samples, or if not available, synthetic contrived specimens using unique negative patient samples.

Second, prior to or concurrent with initiation of testing, the laboratory manufacturer should notify FDA via email to provide applicable test information.

And third, the laboratory manufacturer should prominently disclose in the test report and test ordering information that the test was manufactured for use as 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 and which disease or condition should be identified and that the test has not been reviewed or authorized by FDA.

As discussed earlier, this draft enforcement discretion policy is intended to apply during an emergent situation, which ends when the outbreak or exposure resolves or when an applicable 564 declaration is made.

If no applicable 564 declaration is made within approximately 12 months of the start of an emergent situation, FDA anticipates that the public health rationale for the enforcement policy described in the guidance will no longer apply at that time. Therefore, FDA would expect the laboratory manufacturer to cease offering the immediate response test or seek FDA clearance, approval, or 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, generally around 12 months.

When an applicable 564 declaration is made, the 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 564 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.

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.

Now we'll turn to the details of the Consideration of Enforcement Policies During 564 guidance. When finalized, this draft guidance will describe the factors that FDA intends to consider in determining whether to issue an enforcement policy regarding test manufacturers' offering of certain devices, specifically unapproved tests, for the diagnosis of disease or other conditions during a declared emergency. This draft guidance encompasses considerations that could be applicable to enforcement policies for all test manufacturers, not only laboratory manufacturers.

This draft guidance is consistent with FDA's response to COVID-19 and mpox, where there was a relevant declaration under section 564 and FDA issued guidance with enforcement policies for certain tests to help facilitate availability and quickly increase national testing capacity.

This draft guidance also addresses recommendations from a U.S. Government Accountability Office, GAO, report that reviewed FDA's COVID-19 response and recommended that FDA develop a policy for

the use of enforcement discretion regarding unauthorized tests in future public health emergencies. This policy should include the conditions under which FDA would begin and end the use of such discretion.

Consistent with GAO's recommendation, this draft guidance includes the factors FDA generally intends to consider in developing and issuing any such enforcement policy in future guidance.

In future guidance establishing an enforcement policy for certain tests during a particular 564 declaration, FDA generally intends to include the scope of the enforcement policy regarding certain legal requirements, such as premarket review and quality system requirements; the rationale for the policy; general performance expectations for tests offered as described in the policy; and the intended duration of the policy.

As outlined in this guidance, FDA intends to consider the following factors, among other things, when determining whether to issue an enforcement policy for certain unapproved tests. FDA intends to look at the testing needs of the emergency response. This may include consideration of the number of, and access to, FDA-approved or authorized tests available and how time sensitive the need for a test is. Such as, if there is sufficient time to wait for a test to be cleared, approved, or authorized for emergency use.

In considering the time sensitivity of the need, factors such as the transmission levels, potential for asymptomatic infections, the size of the population potentially exposed, and morbidity and mortality rates may be considered. FDA also may consider the volume of tests needed to address the testing needs, considering the patient populations in need of testing, including estimates based on appropriate modeling for transmission or exposure, and whether the ability to scale up production to account for the needed test capacity should be accounted for in an enforcement policy.

In determining need, FDA also intends to examine the type of test best suited to assist in the response. This may include highly accurate or high-throughput molecular diagnostic tests that can rule out infection, antigen diagnostic tests that may be less accurate but more accessible and less costly, or in rare cases, serology tests that can detect recent infection. Different types of tests may be helpful to the response depending on the type of emergency. Evaluation of need may also include consideration of the turnaround time for results with authorized tests.

FDA also intends to consider the risks to public health when unauthorized, and potentially inaccurate, tests are used. This may include consideration of the seriousness of the life-threatening disease or condition, the complexity of the technology of the test, and the experience of test manufacturers.

FDA intends to look at whether there are appropriate alternatives to diagnose the disease or condition. In considering the adequacy of alternatives, FDA intends to look at the manufacturing capacity of any alternatives and the ability for the alternatives to meet the testing need.

Lastly, FDA intends to consider the availability of other factors that may mitigate the risk of false results from unapproved tests. False results not only negatively impact the individual patient relying on a test but can also have an impact on broad public health decisions during an emergency. FDA may consider factors such as manufacturer experience, participation in a government evaluation program such as the NIH's Independent Test Assessment Program or ITAP, certain validation recommendations, certain labeling statements, the availability of confirmatory testing, public disclosure by manufacturers that the

tests have not been reviewed by FDA, and submission of an EUA request within a reasonable period of time.

Comments for these two draft guidance documents should be submitted by July 5th for consideration in the development of final guidance. Please submit to the appropriate docket number, as shown here.

The next webinar related to LDTs will be in July and will address IVD Classification generally. Please keep an eye on our website for details and submit questions in advance to the email address shown, CDRHWebinars@fda.hhs.gov.

And lastly, here is a list of resources discussed in this presentation. And now I will turn it back over to you, Kim.

CDR Kim Piermatteo: Thank you Toby for that presentation.

We'll now transition to addressing some of your previously submitted questions related to the draft guidances as applicable to IVDs. For this segment, I'll read a question aloud and then Toby will provide a response. As a reminder we will not be taking live questions during today's webinar, therefore, please refrain from raising your hand in Zoom.

Also a reminder as Toby mentioned previously, and I'd like again to remind everyone that we will have our next IVD related webinar in July on the topic of IVD classification. I encourage you to refer to FDA's LDT webpage, specifically the section on webinars, for information on future webinar dates and topics related to IVDs and LDTs. And you will have opportunities to submit questions in advance for possible discussion during a future webinar and details on how to do so will be announced prior to each of those webinar events.

So, Toby, let's get started with questions related to the draft guidance titled, Enforcement Policy for Certain IVDs for Immediate Public Health Response in the Absence of a Declaration under Section 564.

For the first question, Toby, is, how can I determine if a test would fall within the enforcement policy for immediate response tests?

Toby Lowe: Thanks Kim. The Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564 is a draft guidance intended for comment purposes only. When finalized, this guidance will describe FDA's enforcement policy for certain laboratory manufacturers offering certain unauthorized in vitro diagnostic devices for immediate response to CBRN agents, chemical, biological, radiological, or nuclear agents, in the absence of a declaration applicable to IVDs under section 564 of the Federal Food, Drug, and Cosmetic Act.

Following finalization of the guidance, a manufacturer may determine if a test falls within the enforcement policy based on the described scope of the policy. Under the proposed policy, a manufacturer would consider among other things whether the test is manufactured and offered by a laboratory manufacturer as described in Section IV.A of the guidance, and whether the test manufacturer has implemented other key aspects of the policy described in Section IV of the guidance, such as appropriate validation, notification, and transparency.

And as always, FDA is always available to laboratory manufacturers who would like to discuss their planned approach, such as through a pre-EUA submission.

CDR Kim Piermatteo: Thanks Toby. Ok, our next question previously received related to this draft guidance is, how can I find out if there is an emergent situation?

Toby Lowe: An emergent situation, for purpose of this draft guidance, is 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. Laboratories may be among the first to identify an exposure or outbreak through requests for testing and the proposed policy describes circumstances when FDA generally would not object to certain laboratories offering immediate response tests.

As discussed in Section II of the draft guidance and in the preamble to the LDT Final Rule, the enforcement policies discussed in section V.B of the preamble to the LDT Final Rule do not apply to certain tests needed for immediate response to an emergent situation. Based on consultation with CDC, when appropriate, FDA intends to broadly announce when 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.

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, 12 months, excuse me, of the start of an emergent situation.

CDR Kim Piermatteo: Thanks Toby. Ok, so another question that we received is, could an IVD for a CBRN agents fall within any other enforcement discretion policies?

Toby Lowe: Yea, as described in the draft guidance, FDA intends that, in the absence of an emergent situation, including 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, certain LDTs for CBRN agents may fall within the enforcement discretion policies described in section V.B of the preamble of the LDT Final Rule.

CDR Kim Piermatteo: Great, thanks Toby. So two more questions related to this draft guidance, the first one is, what does FDA consider to be appropriately validated for an immediate response test?

Toby Lowe: So as discussed in Section IV.B of the draft guidance, the test should be validated on the test systems intended for clinical use. For example, this would include clinical evaluation and analytical sensitivity, reactivity, and specificity for a PCR-based test for an infectious disease. FDA is available to laboratory manufacturers who would like to discuss their approach for validation in specific circumstances. And additionally, where the need for an immediate response test can be anticipated, we do encourage pre-EUA submissions for preliminary review of available validation information.

CDR Kim Piermatteo: Thanks Toby. So last question on this draft guidance, what steps should a laboratory manufacturer take when an emergent situation ends, and the immediate response test policy no longer applies to the test?

Toby Lowe: Under the proposed policy, if no applicable 564 declaration is made within approximately 12 months of the start of an emergent situation, FDA would expect the laboratory manufacturer to cease offering the immediate response test or submit the test for FDA review through the appropriate regulatory pathway within a reasonable time. FDA would not intend to object to the continued offering of the test during the pendency of the review.

As discussed also in the draft guidance, in Section IV, when an applicable 564 declaration is made, FDA would expect a laboratory manufacturer to cease offering or to submit an EUA request to FDA within approximately 21 days from the date of the declaration and again FDA would not intend to object to the continued offering of the test during the pendency of the review.

As mentioned before, 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.

Additionally, as mentioned earlier, 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, certain LDTs for CBRN agents may fall within the enforcement discretion policies described in section V.B of the preamble to the Final Rule, the LDT Final Rule, sorry.

CDR Kim Piermatteo: Thank you Toby. Ok so then let's move on, let's move on to these next few questions are related to the second draft guidance that is titled, Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency. So we have a few questions on that. The first question, Toby, is what tests are included in the enforcement discretion policies for tests during a Section 564 Declared Emergency? When do the enforcement discretion policies take effect?

Toby Lowe: Thanks Kim, this draft guidance, Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency, does not describe a specific enforcement discretion policy that will go into effect after a 564 declaration. Instead, it describes the factors that, when finalized, FDA intends to consider in determining whether to issue an enforcement policy, considerations for the types of tests and test manufacturers that would be addressed by such an enforcement policy, as well as the circumstances in which the Agency intends to exercise enforcement discretion.

FDA intends to outline any such enforcement discretion policy in a future guidance that identifies, among other things, the intended scope of the enforcement policy regarding certain legal requirements, for example, premarket review, quality system, the rationale for the policy, FDA's general performance expectations for tests offered as described in the policy, and the intended duration of the policy. FDA may also identify any applicable legal requirements that are outside the scope of the enforcement policy, for example complying with applicable medical device reporting or MDR requirements under 21 CFR Part 803.

CDR Kim Piermatteo: Thanks Toby. Our next question related to this draft guidance is, will an enforcement policy be applicable to all IVDs, regardless of the manufacturer?

Toby Lowe: So the Considerations draft guidance encompasses considerations that FDA may decide are appropriate to address in an applicable enforcement policy for certain test manufacturers, which could include both laboratory and non-laboratory manufacturers.

As described in the draft guidance, in determining whether to issue an enforcement policy for certain unapproved tests, FDA intends to assess, among other things the need for accelerated availability of such tests; the known or potential risks of such tests; the availability of appropriate alternative tests that are authorized or approved; and the availability of sufficient mitigations to address risks of false results. And this is all discussed more fully in Section III of the draft guidance.

So as described in the draft guidance, when issuing an enforcement policy, FDA intends to consider the need for certain types of tests best suited to assist in a response, which could apply broadly to all manufacturers of tests or be limited to certain types of manufacturers of tests. And we would intend to outline any such enforcement policy in guidance.

CDR Kim Piermatteo: Thanks again Toby. So, one last question on this draft guidance, and that is, will FDA issue an enforcement policy every time there is a Section 564 declaration related to tests?

Toby Lowe: So as we discussed in the draft guidance, FDA has used its emergency use authority under Section 564 of the FD&C Act to authorize emergency use of IVDs for eight infectious diseases that have emerged over the past 15 years. We have issued enforcement policies during two of the eight emergencies. During the COVID-19 and mpox responses, FDA issued enforcement policies to help supplement the availability of tests when there were insufficient EUA-authorized or FDA-cleared tests to meet demand.

In any declared emergency, FDA intends to consider the factors outlined in the Considerations guidance, when finalized, on a case-by-case basis to determine if it is appropriate to issue an enforcement policy to help quickly increase the national testing capacity and, if so, the scope and appropriate details of such a policy. As well as FDA's general performance expectations for tests offered as described in the policy, and the intended duration of the policy.

So, in the event that FDA determines that it is appropriate to issue an enforcement policy regarding the distribution and use of certain unapproved tests for which EUAs have not been issued, for example, help further expand access to such tests as quickly as possible, FDA intends to outline any such policy in a guidance.

CDR Kim Piermatteo: Great, thanks again Toby. That wraps up our previously submitted questions for today. At this time I'll turn back over to you, Toby, for your final remarks on the draft guidance discussed today.

Toby Lowe: Thanks Kim. Just want to thank everyone again for joining us today. I hope this has been helpful to get a better sense of these two draft guidance documents intended to help support future public health responses through the use of appropriately safe and effective diagnostic tests. We look forward to considering your comments to the docket in the development of final guidances. And hope you all join us for future webinars as well. Thanks Kim.

CDR Kim Piermatteo: Thanks again Toby for those final remarks. For our audience information, printable slides of today's presentation are currently available on CDRH Learn at the link provided on this slide under the section titled In Vitro Diagnostics. And a recording of today's webinar and a transcript will be posted to CDRH Learn under this same section and sub-section in the next few weeks. And a screen shot of where you can find these webinar materials has been provided on this slide as well.

If you have additional questions about today's webinar, feel free to reach out to us in DICE at DICE@fda.hhs.gov.

And lastly, as Toby and I have both mentioned, we hope you're able to join us for our future webinar on IVD Classifications in July. You will be able to find information on how to attend this webinar and any of our upcoming webinars on our CDRH Events page and the link to this page is provided on the bottom of this slide.

Thank you all again for joining us. This concludes today's CDRH webinar. Have a good day.

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