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In response to the United States’ rapidly evolving public health situation, the US Food and Drug Administration (FDA) recently released guidance on high-complexity in vitro diagnostic (IVD) tests for COVID-19. This article provides a high-level overview of regulatory standards for expedited pathways available for COVID-19 vaccine development, and offers an update on COVID-19’s impact on the medical product supply chain and FDA’s proposed mitigations.

IN DEPTH

Laboratory-Developed Test Guidance for COVID-19

On February 20, 2020, FDA issued a Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency:
Immediately in Effect Guidance for Clinical Laboratories and Food and Drug Administration Staff. Under this guidance, labs that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) to perform high-complexity testing may offer *in vitro* diagnostic tests for the detection or diagnosis of COVID-19 while pursuing an Emergency Use Authorization (EUA). An EUA allows continued use of an unapproved product, such as a diagnostic test or vaccine, in response to a public health emergency. The guidance provides minimum validation testing requirements for these diagnostic tests, including specific guidance for limit of detection, cross-reactivity, inclusivity and clinical evaluation.

FDA requests that developers notify the agency once their tests are validated and submit a completed EUA request within 15 business days of validation. While a lab awaits EUA for its test, FDA recommends that the lab send the first five negative and the first five positive specimens for testing using another EUA-authorized assay as an independent check on its validity. FDA is also working with other CLIA-certified laboratories to deploy COVID-19 tests.

While FDA Commissioner Hahn *stated* that the guidance does not change FDA’s standards for issuing EUAs, the guidance is unusual in explicitly announcing that FDA will not take enforcement action on diagnostic tests that are offered as laboratory-developed tests (LDTs). Notably, FDA issued warning letters to several laboratories that offered testing for Zika virus without an EUA during the 2018–2019 outbreak. FDA’s change in course for COVID-19 reflects the difficulty of identifying and isolating coronavirus infections and public laboratories’ potentially limited capability to deploy the quantities of tests currently required.

**Vaccine Development**

In conjunction with the demand for reliable diagnostic tests for COVID-19, stakeholders continue to ask when a vaccine for COVID-19 will become available. Similar to diagnostic tests, FDA may grant an EUA for a COVID-19 vaccine. FDA has various expedited programs that may speed up its review of vaccines in a public health emergency. However, even with the availability of an EUA or an expedited program, developers must meet threshold requirements to demonstrate that a vaccine is safe and effective.

**Vaccine EUA Authorization**

FDA may grant an EUA for a vaccine if it is reasonable to believe, based on the totality of the evidence, including evidence from adequate and well-controlled clinical trials, that:

- The product may be effective in preventing COVID-19.
- The known and potential benefits of the use of the vaccine outweigh the known and potential risks of the product.
- There is no adequate, approved and available alternative to the product for preventing COVID-19.

FDA expects that products manufactured under an EUA will be manufactured in compliance with good manufacturing practices.
Vaccine Expedited Programs

FDA has multiple programs intended to facilitate and speed the review and approval of new therapies for the treatment of serious or life-threatening conditions: Fast Track designation, Breakthrough Therapy designation, Accelerated Approval and Priority Review designation. Developers must demonstrate that they meet the basic regulatory criteria to apply for these programs. A serious disease or condition is “associated with morbidity that has substantial impact on day-to-day functioning” (see 21 CFR § 312.300(b)(1)). A life-threatening condition is a disease or condition “where the likelihood of death is high unless the course of the disease is interrupted . . . and . . . with potentially fatal outcomes, where the end point of clinical trial analysis is survival” (see 21 CFR 312.81(a)). For all of these expedited programs, the applicant must also demonstrate the requisite level of evidence to support the safety and effectiveness of the product at a population level.

FDA has previously granted expedited program designations to therapies for public health emergencies. For example, in December 2019, FDA announced its approval of the first vaccine for the prevention of Ebola virus disease. FDA had granted the applicant Priority Review and Breakthrough Therapy designations. Because of the public health emergency, FDA completed its safety and efficacy evaluation in less than six months and approved the vaccine. As another example, in January 2018, FDA granted Fast Track designation to a Zika virus vaccine in development.

During a public health emergency, a vaccine may receive Accelerated Approval under 21 CFR §§ 601.40 and 601.41 based on adequate, well-controlled clinical trials establishing an effect on a surrogate endpoint (i.e., biological indicators) that is reasonably likely to predict clinical benefit.

In the United States, the Biomedical Advanced Research and Development Authority of the US Department of Health and Human Services, the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health, global nonprofits and private companies are funding vaccine development. On February 25, 2020, the first clinical trial in the United States to evaluate an experimental treatment for COVID-19 began. This clinical trial, sponsored by NIAID and conducted at the University of Nebraska Medical Center, is “a randomized, controlled clinical trial to evaluate the safety and efficacy of the investigational antiviral remdesivir in hospitalized adults diagnosed with COVID-19.” FDA stated that, although “sponsors are usually expected to allow 30 days between submission and initiation of an initial IND protocol to allow for safety review, FDA has been using both pre-IND discussions and highly expedited initial review to allow such trials to begin as soon as possible.”

FDA has expressed a willingness to work with interested sponsors to help expedite the clinical trial process for COVID-19 treatments and products. In a global pandemic, FDA and other US agencies may coordinate with international agencies and review research conducted outside the United States to support approval, and the World Health Organization (WHO) plays a vital role in assessing the ethics of testing in human subjects under the circumstances. For example, in designing its current clinical trial, NIAID leveraged WHO consultations on developing clinical trials for patients with COVID-19 and information regarding study design from the
clinical trials of remdesivir currently ongoing in China.

For any expedited clinical trials, developers are obligated to conduct post-marketing studies to verify the clinical benefit.

**Medical Product Supply Chain**

FDA indicated that it is monitoring how the coronavirus outbreak in China may affect medical product supply chains. Here is the status of key products as of FDA’s most recent update on February 27, 2020:

- **Human Drugs**: Manufacturers of approved human drugs must notify FDA of any anticipated supply disruptions (see 21 CFR § 314.81). To date, FDA has contacted more than 180 manufacturers of human drugs to ask them to evaluate their entire supply chain for ingredients and components sourced from China. FDA also independently identified about 20 non-critical drugs (i.e., drugs that can safely be withheld for a period of time) that solely source their active pharmaceutical ingredients or finished drug products from China. FDA contacted the manufacturers of these drugs to assess whether they face any drug shortage risks, but none have reported such a risk at this time.

- **Biologics and Blood Products**: Manufacturers of licensed biological products also must notify FDA of anticipated supply disruptions (see 21 CFR § 600.82). There are no shortages of biologics at this time, and FDA is not aware of any cellular or gene therapies for the US market that are manufactured in China.

- **Medical Devices**: There is no law requiring medical device manufacturers to report potential shortages or supply chain disruptions, or to otherwise respond to FDA requests for information about potential supply chain disruption. However, FDA has independently identified 62 manufacturers that produce essential medical devices, i.e., those that may be prone to shortage if there is a supply disruption, and is maintaining contact with them. There are currently no reported shortages of these manufacturers’ devices in the United States.

- **Food**: Currently, FDA is not aware of any evidence suggesting that COVID-19 can be transmitted by food or food packaging.

- **Animal Drugs**: FDA has identified 32 animal drug firms that source active pharmaceutical ingredients or finished drugs from China. There are no shortages at this time, but six of the firms have indicated supply chain disruptions could soon lead to shortages.

While the above assessments are focused on China, Dr. Hahn discussed four proposed initiatives in his testimony at the coronavirus hearing before the Senate Committee on Health, Education, Labor and Pensions (HELP Committee) on March 3, 2020, to mitigate or alleviate medical product shortages more broadly:

- **Lengthening expiration dates of human drugs** by giving FDA the authority to require applicants to evaluate, submit studies and label products with the longest possible expiration date to alleviate shortages

- **Improving infrastructure through risk management plans** by giving FDA the authority to require application holders of certain drugs to conduct periodic risk assessments to identify vulnerabilities in their supply chain and develop plans to mitigate such risks
Improving infrastructure through improved data sharing and more accurate supply chain information by giving FDA the authority to require information to assess critical infrastructure, manufacturing quality and manufacturing capacity

Establishing reporting requirements for medical device manufacturers, since, as noted, FDA currently does not have the same authorities for device shortages that it does for drugs and biologics.

The signed appropriations bill to provide emergency funding for the COVID-19 outbreak, the Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020, only provides FDA with funding for “the development of necessary medical countermeasures and vaccines, advanced manufacturing for medical products, the monitoring of medical product supply chains, and related administrative activities.” Congress did not grant FDA explicit authority—including enforcement authority—for the above proposals. The Senate HELP Committee is examining whether to extend these authorities to FDA, and stakeholders should provide comments to committee members.

FDA announced on March 10, 2020, that it is postponing its routine foreign inspections—including pre-approval inspections—through April. FDA will evaluate whether to conduct “for cause” inspections on a case-by-case basis. The agency indicated that the decision was based on a number of factors, including State Department Level 4 travel advisories that prohibit travel for federal employees, Centers for Disease Prevention and Control travel recommendations, entry and access restrictions in foreign countries, and Office of Personnel Management guidance.

FDA is implementing temporary measures to ensure product safety, such as:

- Denying entry of unsafe products into the United States
- Conducting additional physical examinations or product sampling at the borders in cooperation with US Customs and Border Protection
- Reviewing firms’ compliance histories
- Using information sharing with foreign governments based on existing mutual recognition or confidentiality agreements
- Requesting records “in advance of or in lieu of” onsite drug inspections.

FDA also has a risk-based screening tool, PREDICT, which assigns risk scores to focus physical examinations and sample collection. It remains to be seen if and how COVID-19 may affect FDA’s other enforcement and regulatory activities.

Several well-intentioned companies are attempting to develop innovative products to identify or treat COVID-19. FDA and the Federal Trade Commission (FTC) historically have monitored and taken fairly aggressive enforcement action against companies that they view as promoting fraudulent products during outbreak situations, i.e., products that claim to have benefits without approval. As of this writing, FDA and FTC have issued warning letters to seven companies accused of selling unapproved products for the prevention or treatment of COVID-19. FDA stated that it will continue to aggressively monitor the market for fraudulent COVID-19 prevention and treatment claims, and that it will use every authority at its disposal to protect consumers from bad actors. It is important for developers,
including over-the-counter drug developers and developers of artificial intelligence-based diagnostics and patient assessments, to proactively engage with FDA to seek the appropriate approval for their products.

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