COVID-19 vaccines: Dive deep on emergency use authorization

DEC 7, 2020

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Amid widespread vaccine hesitancy that could delay efforts to achieve the herd immunity required to end the COVID-19 pandemic, the top official from the Food and Drug Administration's Center for Biologics Evaluation and Research—Peter Marks, MD, PhD—joined the AMA's president for an in-depth webinar to answer physicians' questions and explain how emergency use authorization (EUA) fits into the coronavirus vaccine-approval process.

Guidance from the FDA states that "issuance of an emergency use authorization requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks." Or, as researchers representing the World Health Organization Solidarity Vaccines Trial Expert Group put it in a *Lancet* commentary: "initial trials comparing COVID-19 vaccines versus placebo should seek reliable evidence not only of some efficacy but of worthwhile efficacy."

EUA is a creation of the post 9/11 environment in 2001. Fears were heightened regarding potential threats such as chemical, biological or radio-nuclear attacks for which there were no FDA-approved medical products available, though some were in development that had potential as treatments.

Before a product can be approved under the EUA process, however, the Health and Human Services secretary is required to first declare that circumstances exist—such as significant potential for a military or public health emergency—to justify issuing the EUA.

Also, there can't be an available alternative product.

Under this rubric, two candidates for FDA authorization as COVID-19 vaccines have been developed expeditiously during the public health emergency. But despite the favorable clinical data touted by their manufacturers, there are understandable questions among the general public—and even health professionals—about the safety and efficacy of vaccines that have been developed and tested in less than a year's time.

So, in addition to evaluating clinical data to determine whether new vaccines are safe and effective, ensuring that what is inside the vaccine packaging "is what it says it is," and monitoring for adverse events once the vaccine is put in use, Dr. Marks said the FDA now finds that reducing vaccine hesitancy has become a significant part of the agency's job.

"What has become really clear during the past year, is that all of these things really feed into what is most important for us, which is helping to ensure public confidence," said the FDA's Dr. Marks, who appeared with AMA President Susan R. Bailey, MD, in the fourth installment of an AMA-hosted " COVID-19: What physicians Need to Know" webinar series to discuss the EUA process and explain how the accelerated approval process is being handled without compromising safety.

Dr. Marks previously appeared with Dr. Bailey in the first webinar, which addressed the COVID-19 vaccine development and the FDA review process for SARS-CoV-2 vaccine candidates. The AMA has made the full webinar, along with a transcript, available.

Read why Dr. Bailey says the effort to restore trust in science must begin now.

Trials lessen tribulations

The FDA issued EUA industry guidance in October, which stated the agency was looking to evaluate products "based on the totality of scientific evidence available, including data from adequate and well controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.

"This standard of 'may be effective' doesn't necessarily breed the kind of confidence that people want to have for a vaccine given to healthy people," Dr. Marks acknowledged. "We recognize that. It's the floor."

The key, he said, was to provide that “clear and compelling efficacy from a large, well-designed phase 3 clinical trial.” And that’s what the first two vaccine candidates—from Pfizer-BioNTech and Moderna—have done by enrolling 43,000 and 30,000 people, respectively, in their clinical trials.

Stay informed by visiting the AMA COVID-19 resource center for physicians.

Why the vaccines are here so fast

In explaining how vaccine development—a process that normally takes several years—is being accomplished in less than 12 months, Dr. Marks noted that traditional vaccine development is a “highly de-risked activity.”

By that, Dr. Marks explained, he means that pharmaceutical companies typically try to cut the cost of research and development by spreading out the risk over time, only advancing from one stage to the next only after they know it is likely the product is going to work.

Manufacturing is often advanced the same way, with the ramping up to commercial-scale production occurring near the end of the process in a similar manner.

What companies did with their potential COVID-19 vaccines was “work at risk,” Dr. Marks said, and began producing millions of vaccine doses without knowing for sure whether their product would be approved.

“That actually saved a significant amount time,” he said, adding that eliminating the normal “dead space” between the three phases of the clinical trial also accelerated the pace of development.

Typically, six months of follow-up study is required after initial vaccine administration during the clinical trial to track adverse events, but this was shortened to two months under the EUA.

Dr. Marks noted, however, that about 95% of serious side effects become apparent within six weeks and that, with trials involving tens of thousands of participants, it the two leading vaccine candidates were severely harming patients, they would have seen evidence by now.

Still, enhanced post-deployment surveillance is a key component of the FDA safety strategy with clinical trial participants being tracked for two years and the FDA and Centers for Disease Control and Prevention both using mega-monitoring systems to watch for problems.

This includes the FDA Sentinel System distributed data network that includes access to very large

databases from which it is able to glean information from claims-based databases covering hundreds of millions of lives.

Learn more about who's first in line for coronavirus vaccines.

Commitment to transparency

Transparency is a key to the FDA's strategy for gaining public confidence in vaccines. Two open meetings of is its Vaccines and Related Biological Products Advisory Committee (VRBAC) will provide the public a look at the data being used to judge potential vaccines' safety and effectiveness.

"We shortened vaccine timelines without compromising vaccine safety and efficacy—we cannot compromise that standard," Dr. Marks said.

The Dec. 10 meeting will cover the Pfizer-BioNTech vaccine, and the VRBPAC panel will meet again Dec. 17 to evaluate the data on the Moderna vaccine.

"One question that will come up is: How fast will we see a vaccine authorized after that?" he said. "It will depend on the discussion at the advisory committee, but we're hoping that, within about a week afterwards, we'll see an authorization for each of those."

By focusing on transparency and addressing concerns about safety and effectiveness, FDA officials hope to show a skeptical public that they are comfortable getting vaccinated themselves and having their families vaccinated as well.

"That has to be really clear, because we hope that we can bring enough people back into the fold for believing this amazing thing we have of vaccines," Dr. Marks said.

Dr. Bailey agreed.

"It's amazing how quickly everything has progressed," the Fort Worth-based allergist and immunologist said. "And the prospect of front-line health care providers and those in long-term care facilities … actually starting the immunization process by the time the holidays roll around—it just gives me goosebumps. It's just absolutely miraculous."