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Science and Evidence-Based Review and Approval of COVID-19 Vaccines: A Statement of Support for the US FDA

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On behalf of the Public Policy Committee of the American College of Clinical Pharmacology

The coronavirus disease 2019 (COVID-19) pandemic, the most critical international health emergency in a century, has claimed 1.4 million lives worldwide, with approximately 260 000 in the United States alone as of November 24, 2020.[1] With resurgence of infection rates currently underway in many parts of the world, including the United States, the number of deaths will continue to increase. The transmission rate and rapid spread of the severe acute respiratory syndrome coronavirus 2 resulting in the ongoing pandemic has undoubtedly created an emergency that demands rapid development of safe and effective therapies and vaccines in parallel with evolving knowledge and understanding of the disease itself. This urgency and rapid evolution of knowledge has put unprecedented pressure on the scientific and medical community to find therapeutic and preventive options and on the US Food and Drug Administration (FDA) to approve them.

To fast-track vaccine development and distribution, a public-private partnership (Operation Warp Speed) of US government agencies (eg, Health and Human Services, Department of Defense) and private enterprises was launched in May 2020. The partnership uses government infrastructure and resources to accelerate simultaneous development and manufacture of multiple vaccine candidates based on several technology platforms, with the objective of rapid deployment of safe and effective FDA-authorized vaccines to the US population.[2,3]

Whereas Operation Warp Speed addresses logistical, financial, and other aspects to accelerate vaccine development, production, and deployment, it is imperative to recognize that approval or authorization rests solely with the FDA and shall follow existing, well-established, time-tested, science- and evidence-based processes, including risk-benefit assessment by independent advisory committees of nongovernment scientists, physicians, and other experts.[4] To allay concerns of external interference in approval or authorization processes, the leadership of the FDA emphasized that "COVID-19 vaccines will be reviewed according to established legal and regulatory standards."[5] Assuring the US public that vaccine review and approval processes will be based on transparency, sound science, and scientific integrity, and according to federal statute and established FDA regulations, will enhance confidence and facilitate uptake of therapies by the public. These elements are critical for effective management of the pandemic.

For decades, the FDA has maintained the trust of the US public in making independent, rigorous, and

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*This position paper is dedicated to the memory of Dr. Hartmut Derendorf, who contributed to its inception and writing and passed away suddenly on November 23, 2020.

science-based assessments and decisions with regard to the totality of available evidence for the efficacy and safety of drugs and vaccines evaluated for approval in the United States. Because of dedicated efforts by FDA scientists, physicians, career officers, and administrators, the FDA has established a world-class reputation in carrying out its mandate of protecting public health. Focused on improving their success at an even better rate, the FDA has increasingly approved drugs based on fewer clinical trials and use of surrogate endpoints[6] and has given the most approvals for novel entities compared to other regulatory authorities.[7]

As of this writing, there are at least 5 vaccine trials in phase 3 and multiple other trials in phase 1/2 stages of development in the United States.[8] To ensure evidence-based approval of vaccines, the FDA recently committed to assuring that manufacturing meets its quality standards and that vaccine effectiveness and safety are verified.[5] To guide vaccine developers on FDA expectations for approval, a final guidance for approval was issued by the FDA in June 2020.[9] The guidance is comprehensive and addresses specific aspects related to enrolling diverse populations (ie, racial and ethnic minorities), including the elderly, those with comorbidities, and relevant subpopulations. For appropriate assessment of efficacy, the guidance recommends that best practices should be followed for trial design, specifically that phase 3 trials should be randomized, double-blind, and placebo-controlled, with sample sizes and timing of interim analyses based on statistical success criteria for primary and applicable secondary endpoints. To ensure effectiveness after wide deployment, the guidance explicitly states that the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is $>30\%$ (ie, the lower limit of the 95% confidence interval should be $>30\%$).[9] Despite the absence of historical precedence in prospectively recommending numerical endpoints for approval, the FDA has defined these outcome expectations in the belief that "a baseline for performance is necessary to provide confidence that broad distribution of a potential vaccine could offer immunity to the majority of the population."[5] Safety aspects are likewise comprehensively addressed, including vaccine-associated enhanced respiratory distress; postmarketing surveillance aspects need to be discussed with the FDA before approval.

It is important to recognize that the final guidance with clear thresholds around efficacy endpoints (and methodology aspects described above) was issued *prior* to the initiation of most large-scale vaccine trials. This was done proactively to ensure that a safe and effective COVID-19 vaccine meets or exceeds FDA standards for approval and meaningfully aids in the pandemic recovery.[5] Recently, recognizing that an Emergency Use Authorization may be requested based on interim results from ongoing vaccine trials, the FDA issued guidance (October 2020) for emergency authorization to enable rapid and widespread deployment after determining the vaccine's efficacy and safety from at least one phase 3 trial in a compelling manner.[10] This includes meeting the prespecified success criteria for the primary endpoint as described in the final guidance for approval,[9] a median safety follow-up period of at least 2 months after completion of the vaccination regimen, and other requirements necessary to enable the FDA to make an appropriate risk-benefit assessment. Further, evaluation of safety and efficacy by the Vaccines and Related Biological Products Advisory Committee that is open to the public will lend further transparency to the authorization process.

In summary, despite the unprecedented COVID-19 health emergency, the US FDA has endeavored to be transparent and base decisions grounded in science- and evidence-based approaches. Further, while working alongside other federal and private organizations, the FDA has made clear its position regarding its independence in making approval or authorization decisions. The FDA has been proactive and has taken appropriate steps in issuing approval and authorization guidance documents with design, efficacy, and safety considerations to facilitate industry understanding of FDA expectations. These proactive and science-based approaches will certainly facilitate the review and approval or authorization processes, especially with data from multiple vaccine trials starting to emerge, and clear, transparent decisions are necessary for deployment and public acceptance of vaccines. The American College of Clinical Pharmacology believes that these nonpartisan and transparent approaches are the foundations of the FDA's long-standing mandate of protecting public health in the United States, and that the FDA strives to continue to follow its mandate during this health emergency of immense proportions. The American College of Clinical Pharmacology fully supports and commends the US FDA in its endeavor to approve or authorize vaccines on the basis of science- and evidence-based approaches for the prevention of COVID-19.

Conflicts of Interest

Dr. Pai is an employee of Akros Pharma Inc. Dr. Othman is an employee and shareholder of Gilead Sciences, Inc. Dr. Rusch is an employee of Celerion. Dr. Masters is an employee and shareholder of Pfizer, Inc. Dr. Greene is an employee and shareholder of Kura Oncology. Dr. Rogge is an employee and shareholder of Takeda Pharmaceuticals International Co. Dr. Gries is an employee and shareholder of Kodikaz

Therapeutic solutions, a scientific advisory board member of Feldan Therapeutics, and a shareholder of LabCorp, Novartis and Alcon. Dr. Clementi is the president of Clementi Ltd, an independent consulting firm, and does not represent clients with a vaccine in Phase III trials. Dr. Kumar is an employee of Otsuka Pharmaceutical Co. Dr. Younis is an employee of Astellas Pharma, Inc. Dr. Salem is an employee and shareholder of AbbVie. Drs. Gaynes and Pastino report no relevant disclosures.

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