

## COVID-19 Vaccines: Ensuring Regulatory and Scientific Integrity During the Approval Process

Nicholas R. Harrison, Adam Kroetsch, William Bleser,  
Morgan Romine, and Mark McClellan

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### *Introduction*

The ready availability of one or more safe and effective vaccines for COVID-19 is a critical component of overcoming the current pandemic. While an unprecedented global effort is underway to research and develop COVID-19 vaccines, U.S. decision-makers and the broader American public are focusing considerable attention on the U.S. Food and Drug Administration's (FDA) well-established regulatory steps to evaluate the data and evidence on potential vaccines and approve them for human use.

FDA has two pathways for reviewing and approving vaccines—the traditional Biologics License Application (BLA) pathway and Emergency Use Authorization (EUA), an abbreviated pathway that allows the agency additional flexibility and discretion during a public health emergency. An EUA may permit use among specific, limited populations while data and evidence are generated to support full BLA approval.

This issue brief outlines the key scientific and evidentiary standards that the FDA will apply to vaccine review, as well as the multiple safeguards in place to ensure that the overall process is scientifically credible and can be trusted by the broader public.

### *Standards for FDA Authorization or Approval of COVID-19 Vaccines*

In recent weeks, [career officials](#) at the FDA have repeatedly [made clear](#) that they will not authorize or approve a COVID-19 vaccine without strong data showing that it is safe, effective, and manufactured to a high-quality standard. **The process by which the FDA's expert review staff and independent advisors will make this determination is based in decades of well-established regulatory processes, including multiple public-facing steps to ensure transparency.** All of these steps will take place regardless of whether a vaccine is under review for full approval under a traditional BLA or for authorization under an EUA.

Because the FDA anticipates that the first COVID-19 vaccines are likely to be made available under an EUA in the near term, there has been understandable public scrutiny of the integrity and safeguards in place for this pathway. In [initial guidance](#) published in June 2020 and [additional formal guidance](#) released in October, the agency reaffirmed its commitment to long-held gold standards for assessing vaccine safety and efficacy. The FDA also committed in these documents

to apply an “EUA-plus” standard to the review of potential COVID-19 vaccines that will require vaccine manufacturers to demonstrate safety and efficacy for an EUA similar to that expected during the review of a full BLA request.

Accordingly, the FDA expects any EUA or BLA filed for a COVID-19 vaccine to meet the following criteria:

- **Clear and compelling evidence of vaccine effectiveness from large, well-designed phase 3 clinical trials**—including significant reductions in COVID-19 infection as measured by reliable clinical endpoints, as well as additional data regarding COVID-19 disease severity and COVID-19 disease among older clinical trial participants.
- **At least 50% efficacy as measured by the primary efficacy outcome**—meaning that the proportion of clinical trial participants with laboratory-confirmed COVID-19 or SARS-CoV-2 infection should be at least 50% lower in the vaccinated group than in the placebo group. Importantly, the primary efficacy outcome to support an EUA will not differ from the primary efficacy outcome studied as part of a completed phase 3 clinical trial to support a full BLA. Furthermore, the FDA has said that phase 3 clinical trials must be designed to provide assurance (based on the lower bound of an appropriately adjusted confidence interval) that efficacy is unlikely to be any less than 30%.
- **Availability of well-characterized safety data**—expected to comprise the outcomes of at least 15,000–20,000 clinical trial participants with a median follow-up period of two months for an EUA, and tens of thousands of participants over the course of at least a year for a full BLA. Importantly, the degree of safety data required for a COVID-19 vaccine EUA is closer to what would typically be included within a BLA, and is well beyond the safety data typically required for an EUA in other specific therapeutic or disease contexts in which a treatment has previously been characterized for other uses.

The FDA is also already working with manufacturers to design robust pharmacovigilance plans to monitor vaccine safety following an authorization or approval. These plans extend vaccine safety monitoring by six months to a year or longer, ensuring that even rare adverse events will be identified and responded to appropriately. And, before any COVID-19 vaccine is available, the FDA will evaluate the manufacturing process by which they are made to ensure quality, consistently, and reproducibly.

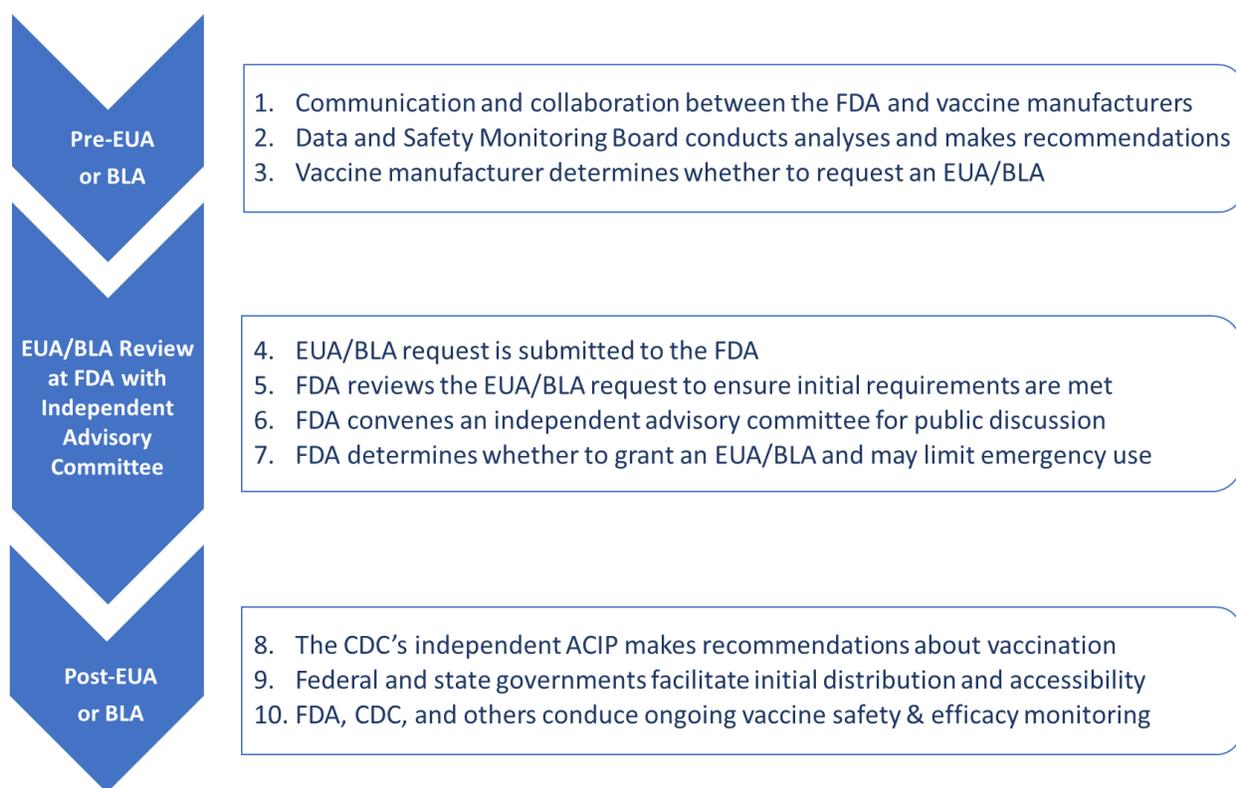
### *Safeguards in the Vaccine Evaluation and Approval Process*

Beyond the FDA’s expert review process described above, both manufacturers and their Federal counterparts at the FDA and Centers for Disease Control and Prevention (CDC) follow additional established steps in the vaccine evaluation process that incorporate transparent decision-making and ensure scientific integrity.

During late stage development, vaccine manufacturers follow the advice of independent **Data and Safety Monitoring Boards (DSMBs)** to determine when data from phase 3 clinical trials supports requesting an EUA or BLA. Every clinical trial involves an independent DSMB, which is

made up of outside experts in academic and scientific research, clinical care, and ethics who are charged with reviewing incoming trial data before it is seen by the manufacturer.<sup>1</sup> This structure empowers the DSMB to conduct analyses to assess whether the clinical trial demonstrates efficacy. In the case of COVID-19 vaccines, if a DSMB analysis shows substantial vaccine efficacy as described in FDA guidance, the DSMB is likely to recommend the manufacturer submit an EUA or BLA request.

Once an EUA or BLA request is made, the FDA will convene an independent [advisory committee](#) that will review the analysis of FDA career staff to determine whether the evidence submitted warrants issuing an EUA or BLA. This independent advisory committee, the **Vaccines and Related Biologic Products Advisory Committee (VRBPAC)**, will make a formal recommendation on whether a vaccine should be authorized or approved, and may also recommend that manufacturers collect additional data following an authorization or approval. Importantly, VRBPAC will review the data and evidence and deliberate in a public meeting that ensures transparency and credibility.



**Figure 1: The vaccine evaluation process in the context of an EUA or BLA request**

<sup>1</sup> A common DSMB convened by the National Institutes of Health (NIH) is monitoring all phase 3 COVID-19 vaccine clinical trials supported through Operation Warp Speed, including the clinical trials being sponsored by Moderna, Johnson & Johnson, and AstraZeneca. Members are paid \$200 per meeting. Pfizer supports its own five-member COVID-19 vaccine DSMB.

If the FDA issues an EUA or BLA, the vaccine will be made available following additional deliberation about its appropriate use and distribution by the CDC's **Advisory Committee on Immunization Practices (ACIP)**. ACIP is comprised of medical and public health experts who review the data and evidence that was provided to the FDA, as well as the specifics of VRBPAC's recommendations and the FDA's approval for specific populations, to further develop recommendations on the use of a vaccine. Through meetings open to the public, ACIP will provide guidance on the appropriate use of authorized vaccines, potential prioritization among specific groups (for example, older adults), and areas where more data or evidence are needed. Expert groups including the National Academy of Medicine (NAM) have already published [key considerations and recommendations](#) likely to contribute to the ACIP's decision-making.

Once recommendations regarding effective vaccinations are in place, Federal and state agencies will enact plans and infrastructure to deliver and distribute authorized COVID-19 vaccines. Distribution will be guided both by Federal recommendations as well as by decisions made by state and local leaders. Initially, supplies of authorized COVID-19 vaccines may be limited, underscoring the importance of thoughtfully considered plans to prioritize vaccinations.

Finally, Federal and state agencies and their health care partners in the private sector will track COVID-19 vaccination data. This data will be used to ensure individuals are able to complete multi-dose vaccination schedules successfully and to continue monitoring vaccination outcomes for safety and efficacy. This data is expected to inform the deployment of resources to quickly provide accessible vaccinations to those at highest risk of getting sick or dying from COVID-19, particularly healthcare workers, essential workers, and those within communities of color. A companion Duke-Margolis primer on vaccine distribution and access challenges can be found [here](#).

### ***Conclusion***

The processes and safeguards outlined above have been the foundation for trusted use of medical products in the United States for decades. They have been designed to meet this moment, and have repeatedly formed the backbone of public statements and commitments to scientific rigor and transparency made by vaccine developers and career staff and leadership at the FDA and CDC. So long as these experts and officials continue to meet such long-held standards, Americans can trust that any vaccine made available to the public will be safe and effective.

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### *Author Affiliations*

Mr. Harrison is a Senior Research Assistant at the Duke-Margolis Center for Health Policy.

Mr. Romine is a Policy Fellow at the Duke-Margolis Center for Health Policy.

Mr. Kroetsch is a Research Director at the Duke-Margolis Center for Health Policy.

Dr. Bleser is a Managing Associate at the Duke-Margolis Center for Health Policy. He has previously received consulting fees from Merck on vaccine litigation unrelated to this work and serves as Board Vice President (uncompensated) for Shepherd's Clinic, a clinic providing free healthcare to the uninsured in Baltimore, MD

Dr. McClellan, who directs the Duke-Margolis Center for Health Policy, was Commissioner of the Food and Drug Administration from 2002-04 and Administrator of the Centers for Medicare and Medicaid Services from 2004-06. He is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomIQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.