FDA Issues New Guidance to Developers of COVID-19 Vaccines

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On June 30, 2020, the U.S. Food and Drug Administration (FDA) released new guidance to provide recommendations for sponsors to facilitate development of SARS-CoV-2 vaccines to prevent COVID-19. The guidance highlights key requirements for conducting clinical trials under Investigational New Drug applications (IND), for chemistry, manufacturing, and controls (CMC) requirements in manufacturing, nonclinical and clinical data needs, as well as post-market safety monitoring. [1] Like other COVID-19 guidance documents, the FDA is implementing the guidance without public comment.

FDA notes that "[t]here are many COVID-19 vaccines currently in development," and the Biotechnology Industry Organization (BIO) COVID-19 dashboard notes 161 vaccine candidates under development worldwide as of June 21, 2020. [2] On June 30, Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NAID), National Institutes of Health (NIH), confirmed in Senate testimony that vaccine candidates would be beginning phase 3 studies this summer, [3] which are expected to include "30,000 people to test a government-created shot starting in July." [4]

Much of the FDA guidance restates the current, standing requirements for vaccine licensure under the Public Health Service (PHS) Act and the Federal Food, Drug and Cosmetic Act (FFDCA), but includes notable novel observations, such as:

- **Emergency Use Authorization.**FDA states that an EUA "may be appropriate… once studies have demonstrated the safety and effectiveness of the vaccine but before the manufacturer has submitted and/or FDA has completed its formal review" of a BLA, in order to avoid detrimentally affecting the conduct or completion of "large randomized clinical efficacy trials … to demonstrate effectiveness." [5]
- **Clinical endpoints.** According to FDA, with "no accepted surrogate endpoints" for COVID-19, sponsors "should … pursue traditional approval via **direct evidence of vaccine safety and efficacy.**" [6] Either laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection is an acceptable primary endpoint for efficacy trials. [7]
    - FDA notes that, in the future, "**accelerated approval** of a COVID-19 vaccine … may be considered" as "additional understanding of SARS-CoV-2 immunology, and specifically vaccine immune responses" becomes available. [8]
- **Clinical trials.**FDA states that for "a widely deployed COVID-19 vaccine" to be deemed effective, its efficacy trials should have a primary endpoint of **50% success over placebo**. [9]
    - The Agency also offers "early advice, and potentially concurrence in principle, on plans for **expedited/seamless clinical development**" provided data summaries are provided "at each development milestone for FDA review and concurrence prior to advancing to the next phase of development." [10]"The size of the **safety database**" for a COVID-19 vaccine "should be no different than for other preventive vaccines for infectious diseases," which FDA notes typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure." [11]
    - Sponsors should expect **late-stage** clinical trials to be "randomized, double-blinded, and placebo controlled" [12] and to "likely need to enroll **many thousands of participants**, including many with medical comorbidities for trials seeking to assess protection against severe COVID-19." [13]
    - The guidance specifically emphasizes the importance of collection of preliminary **safety and immunogenicity data** for each dose level and age group, of **pediatric** investigations, the inclusion of diverse populations, and exclusion of **vulnerable populations** and individuals with **acute COVID-19** from enrollment. [14]

- **Manufacturing.** FDA signals its willingness to accept reliance on previously licensed vaccine platforms, stating that COVID-19 vaccine development "may be accelerated based on knowledge gained from similar products manufactured with the same **well-characterized platform technology**, to the extent legally and scientifically permissible." "**Complete details,**" however, of manufacturing must be provided in the Biologics License Application (BLA) at time of filing, including "critical process parameters, critical quality attributes, batch records, defined hold times, and the in-process testing scheme." [15]
- **Nonclinical and toxicity studies.** FDA encourages "**early communications**" on required nonclinical testing. [16] Separately, FDA notes that such studies should account for theoretical risks of COVID-19 vaccine-associated **enhanced respiratory disease** (ERD), and developmental and reproductive toxicity (DART) studies be conducted in women of childbearing potential. [17]The Agency notes again the potential impact of platform technologies, including the possible **waiver** of nonclinical safety studies and DART studies where use of such technology underlying a licensed vaccine may provide "adequate information to characterize product safety."
- **Post-market safety.**Noting the importance of pharmacovigilance, FDA states that "[f]ollow-up of study participants for COVID-19 outcomes (in particular, for severe COVID-19 disease manifestations) should continue as long as feasible, ideally at least one to two years." [18]The Agency also recommends inclusion of a Pharmacovigilance Plan (PVP) at time of BLA filing, and restates its authority to mandate postmarketing studies. [19]

Foley Hoag has formed a firm-wide, multi-disciplinary task force dedicated to client matters related to the novel coronavirus (COVID-19). For more guidance on your COVID-19 issues, visit our Resource Portal or contact your Foley Hoag attorney.

[1] FDA, Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19, June 30, 2020, available at https://www.fda.gov/media/139638/download

[2] BIO, COVID-19 Therapeutic Development Tracker, accessed June 30, 2020, at https://www.bio.org/policy/human-health/vaccines-biodefense/coronavirus/pipeline-tracker

[3] Senate HELP Committee, Hearing: COVID-19: Update on Progress Toward Safely Getting Back to Work and Back to School, June 30, 2020.

[4] L. Neergard, Associated Press, Summer may decide fate of leading shots in vaccine race, June 28, 2020.

[5] Guidance at 19.

[6] *Id.* at 2 and 9.

[7] *Id.* at 13.

[8] *Id.* at 18.

[9] *Id.* at 14.

[10] *Id.* at 9.

[11] *Id.* at 15.

[12] *Id.* at 12.

[13] *Id.* at 10.

[14] *Id.* at 10-11.

[15] *Id.* at 3.

[16] *Id.* at 6.

[17] *Id.* at 7.

[18] *Id.* at 12.

[19] *Id.* at 17.

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