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Emergency Use Authorization for Vaccines to Prevent COVID-19

Guidance for Industry

Document issued on March 31, 2022.

**This document supersedes the guidance of the same title issued on
May 25, 2021.**

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number FDA-2020-D-1137 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," available at <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>, and from the FDA webpage titled "Search for FDA Guidance Documents" available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

Additional copies of this guidance are also available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>.

Questions

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA plays a critical role in protecting the United States (U.S.) from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide sponsors of requests for Emergency Use Authorization (EUA) for COVID-19 vaccines with recommendations regarding the data and information needed to support the issuance of an EUA under section 564 of the FD&C Act (21 U.S.C. 360bbb-3) for an investigational vaccine to prevent COVID-19 for the duration of the COVID-19 public health emergency. This document supersedes the guidance of the same title issued in May 2021 (which superseded the guidance of the same title issued October 2020 and reissued February 2021).

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)).

Given this public health emergency, and as discussed in the Notice published in the *Federal Register* of March 25, 2020, titled “Process for Making Available Guidance Documents Related to Coronavirus Disease 2019,” (85 FR 16949) available at <https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf>, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency’s good guidance practices.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance

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documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

There is currently a respiratory disease pandemic caused by a novel coronavirus. The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.¹ In addition, on March 13, 2020, there was a Presidential declaration of a national emergency in response to COVID-19.²

The COVID-19 pandemic presents an extraordinary challenge to global health. Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates using different technologies including RNA, DNA, protein, and viral vectored vaccines.

This guidance was first developed prior to issuance of an EUA or license for a COVID-19 vaccine but has been revised to take into account the EUAs currently in place for COVID-19 vaccines and the U.S.-licensed vaccines for the prevention of COVID-19. This guidance describes FDA’s current recommendations regarding the data and information needed to support the issuance of an EUA under section 564 of the FD&C Act (21 U.S.C. 360bbb-3) for an investigational vaccine to prevent COVID-19, including chemistry, manufacturing, and controls information (CMC); nonclinical data and information; and clinical data and information, as well as administrative and regulatory information. In addition, the guidance provides recommendations regarding key information and data that should be submitted to a relevant investigational new drug application (IND) or cross-referenced master file (MF) prior to submission of an EUA request in order to facilitate FDA’s complete and timely review of such a submission, including convening the Vaccines and Related Biological Products Advisory Committee (VRBPAC). This guidance also discusses FDA’s current thinking regarding the circumstances under which the issuance of an EUA for a COVID-19 vaccine would be appropriate, providing additional context to the discussion regarding EUAs in the guidance for industry entitled “Development and Licensure of Vaccines to Prevent COVID-19” (Ref. 1).

These recommendations are specific to COVID-19 vaccines, which are complex biological products that are intended to be administered to millions of individuals, including healthy people, to prevent disease. These vaccines have the potential for broad use under an EUA. The recommendations in this guidance are not necessarily applicable to drugs and biological products intended for treatment of COVID-19, for which there may be significantly different considerations under the standard set forth in section 564 of the FD&C Act (21 U.S.C. 360bbb-3), reflecting the products’ characteristics

¹ Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

² Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), available at <https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>. On February 24, 2021, there was a Presidential Declaration continuing the national emergency concerning the COVID-19 pandemic beyond March 1, 2021. *See* Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic (Feb. 24, 2021), available at <https://www.federalregister.gov/documents/2021/02/26/2021-04173/continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019-covid-19-pandemic>.

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and anticipated clinical uses.

Sponsors engaged in the development of vaccines to prevent COVID-19 should refer to the guidance for industry entitled “Development and Licensure of Vaccines to Prevent COVID-19” (Ref. 1), the guidance for industry and investigators entitled “COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products” (Ref. 2), and the guidance for industry and other stakeholders entitled “Emergency Use Authorization of Medical Products and Related Authorities” (Ref. 3).

III. CRITERIA AND CONSIDERATIONS FOR THE ISSUANCE OF AN EUA FOR A COVID-19 VACCINE

On February 4, 2020, pursuant to section 564(b)(1)(C) of the FD&C Act (21 U.S.C. 360bbb-3(b)(1)(C)), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the virus that causes COVID-19. On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. 360bbb-3(b)(1)).³

Based on this declaration and determination, FDA may issue an EUA after FDA has determined that the following statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)) (Ref. 3):

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- 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.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.⁴

³ This EUA declaration is distinct from, and is not dependent on, the declaration by the Secretary of HHS of a public health emergency related to COVID-19, issued on January 31, 2020, and subsequently renewed, under section 319 of the PHS Act. *See supra* note 1. The issuance of an EUA for a COVID-19 vaccine is not based on that January 2020 declaration of a public health emergency and, therefore, an EUA may remain in effect beyond the duration of the public health emergency declaration if all other statutory conditions are met.

⁴ For example, a potential alternative product may be considered “unavailable” if there are insufficient supplies of the approved alternative to fully meet the emergency need. *See* section III.B.1.d of “Emergency Use Authorization of Medical Products and Related Authorities” guidance (Ref. 3).

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In the case of investigational vaccines being developed for the prevention of COVID-19, any assessment regarding an EUA will be made on a case-by-case basis considering the target population, the characteristics of the product, the preclinical and human clinical study data on the product, and the totality of the available scientific evidence relevant to the product.

FDA acknowledges that an EUA for a COVID-19 vaccine may be requested to allow for the vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people, potentially following interim results from one or more clinical trials meeting pre-specified success criteria described in the analysis plan submitted to FDA. In this scenario, for a COVID-19 vaccine for which there is adequate manufacturing information to ensure quality and consistency, issuance of an EUA would require a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.

It is FDA's expectation that, following submission of an EUA request and issuance of an EUA, a sponsor would continue to collect data in any ongoing trials and would also work towards submission of a Biologics License Application (BLA) as soon as possible⁵. FDA's recommendations regarding the safety and effectiveness data and information outlined in section VI of this guidance are essential to ensure that clinical development of a COVID-19 vaccine has progressed far enough that issuance of an EUA for the vaccine would not interfere with the ability of an ongoing Phase 3 trial to demonstrate effectiveness of the vaccine to support licensure and to continue safety assessments, including investigating the potential for vaccine-associated enhanced respiratory disease (ERD). The ability of a sponsor to accrue this information about a COVID-19 vaccine is critical to ongoing assessment of its benefits and risks. FDA notes that there would need to be an adequate plan for safety data collection among individuals vaccinated under an EUA.

IV. KEY LOGISTIC RECOMMENDATIONS FOR THE REQUEST FOR AN EUA FOR A COVID-19 VACCINE

A sponsor⁶ considering the submission of an EUA request for an investigational COVID-19 vaccine should contact the Center for Biologics Evaluation and Research's (CBER's) Office of Vaccines Research and Review (OVRR) as early in development as possible to discuss expectations and considerations for the sponsor's particular vaccine.

FDA also recommends that vaccine sponsors engage in early communication with CBER's Office of Compliance and Biologics Quality (OCBQ), Division of Manufacturing and Product Quality to discuss facility issues related to manufacturing of the particular vaccine.

⁵ In earlier versions of this guidance, FDA included language stating that it expected sponsors to continue to collect placebo-controlled data in an ongoing trial for as long as feasible after submission of an EUA request and issuance of an EUA. FDA has modified this language because access to a safe and effective authorized or approved COVID-19 vaccine may preclude the ethical continuation of blinded, placebo-controlled follow-up in ongoing clinical trials. Additionally, trial participants may choose to withdraw from trial follow-up for any reason, including to receive a vaccine available to them under an EUA.

⁶ For purposes of this guidance, the term "sponsor" is used when referring to the applicant, submitter, or person requesting an EUA.

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In order to facilitate a complete and timely review of a request for an EUA for a COVID-19 vaccine, including scheduling of a meeting of FDA's VRBPAC, the following information should be submitted in advance of submission of an EUA request:

- A detailed description of the chemistry, manufacturing, and controls information and data described in section VI.B of this guidance should be submitted to a relevant IND or cross-referenced MF(s) at least one month prior to submission of an EUA request.
- FDA strongly encourages the vaccine sponsor to provide FDA with notice within 24 hours after any interim analysis has been completed, on the basis of which submission of an EUA request is planned, by contacting OVRP, and to discuss proposed timelines for submission of an EUA request.

V. PRIORITIZATION OF REQUESTS FOR ISSUANCE OF AN EUA FOR A COVID-19 VACCINE

The issuance of an EUA is discretionary. FDA's decision to review and process an EUA request, and ultimately issue an EUA if the relevant statutory criteria are met, is based on a determination, on a case-by-case basis, that such action is necessary to protect the public health in an emergency. It is an authorization that the government "may" issue when necessary to protect the public health in an emergency (see section 564 FD&C Act (21 U.S.C. 360bbb-3(a)(1)), which states, in relevant part, "subject to the provisions of this section, the Secretary may authorize the introduction into interstate commerce...a drug, device, or biological product intended for use in an actual or potential emergency"). FDA's January 2017 guidance entitled, "Emergency Use Authorization of Medical Products and Related Authorities," (Ref. 3) describes factors that FDA intends to use in its prioritization of EUA requests, such as the public health need for the product, the availability and adequacy of the information concerning the likelihood that the product may be safe and effective in preventing, treating, or diagnosing the condition, and whether the product is included in government stakeholder stockpiles.

When FDA assesses investigational COVID-19 vaccines for use under EUA, FDA's review includes: stringent evaluation of product quality, including a determination that the facilities producing the product meet appropriate standards; evaluation of the conduct of clinical trials; and assessment of trial data integrity. As noted in section IV of this guidance, early interaction with the Agency is critical. FDA intends to decline to review and process EUA requests in cases where it is not feasible for the Agency to verify any one of these characteristics. Additionally, given the need to address urgent public health priorities, FDA may need to further prioritize among the EUA requests it receives for COVID-19 vaccine candidates. For the remainder of the current pandemic, FDA may decline to review and process further EUA requests other than those for vaccines whose developers have engaged in an ongoing manner with the Agency during the development of their manufacturing process and clinical trials program as described in this guidance, "Emergency Use Authorization for Vaccines to Prevent COVID-19." These COVID-19 vaccine developers will have had the benefit of FDA feedback early and throughout the development process. Therefore, their EUA requests are more likely to contain the comprehensive data and information needed to demonstrate that issuance of an EUA is appropriate, and the Agency is more likely to be able to confirm the validity of the clinical and manufacturing information submitted in the EUA request.

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VI. RECOMMENDATIONS REGARDING INFORMATION AND DATA TO BE INCLUDED IN A REQUEST FOR AN EUA FOR A COVID-19 VACCINE

As stated in the “Emergency Use Authorization of Medical Products and Related Authorities” January 2017 guidance (Ref. 3), FDA recommends that a request for an EUA include a well-organized summary of the available scientific evidence regarding the product’s safety and effectiveness, risks (including an adverse event profile) and benefits, and any adequate, approved, available alternatives to the product. FDA recommends that the following information be submitted in a request for an EUA for a COVID-19 vaccine or, as applicable, that this information be submitted in a relevant IND or cross-referenced MF before an EUA request is submitted.

A. Regulatory

The following information should be submitted in a request for an EUA for a COVID-19 vaccine:

1. A description of the product and its intended use (e.g., identification of the serious or life-threatening disease or condition for which the product may be effective; where, when, and how the product is anticipated to be used; and/or the population(s) for which the product may be used). The submission should address the following details:
 - Proposed use(s) under EUA
 - Proposed dosing regimen(s) and method(s) of administration for use under EUA
 - Rationale for dosing regimen
 - Information to support the use, dosing and administration of the vaccine in the following populations, as applicable:
 - Adults
 - Pediatric age groups
 - Other specific populations (e.g., geriatric individuals, pregnant or lactating individuals, immunodeficient individuals);
2. Available safety and effectiveness information for the product;
3. A discussion of risks and benefits, including available information concerning the threat posed by SARS-CoV-2 and how that threat would be addressed by the product under the proposed use under the EUA. As noted above, for a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine’s benefits and risks and support issuance of an EUA would include not only meeting the prespecified success criteria for the study’s primary efficacy endpoint, but also additional safety and effectiveness data as described below in section VI.C.3 of this guidance. The discussion of the risks and benefits in the EUA request should include an assessment of the risks and benefits for the proposed use under the EUA, including a discussion of the following:
 - Any steps taken to mitigate risk or optimize benefit
 - Any recommended restrictions to ensure safe use
 - Any situations under which the product should not be used (i.e., contraindications)
 - Important information that should be considered prior to use of the EUA product;

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4. The need for the product, including identification of any approved alternative product(s) and their availability and adequacy for the proposed use;
5. A description of the product's FDA approval status; whether the product is under an investigational application (e.g., if an IND is in effect or has been submitted); whether the product is approved in a foreign country for either the proposed use or another use; and information on the use of the medical product by either a foreign country or an international organization (e.g., the World Health Organization (WHO)). The submission of the EUA request should include a brief summary of any related submissions to FDA and indicate which one(s) were cross-referenced in a letter to this file. This information may include:
 - Related IND number(s) and a brief description of the stage of clinical testing
 - Related Pre-IND number(s)
 - Related MF number(s) and brief description of the contents;
6. Information comparable to an FDA-approved package insert; drafts of the "Fact Sheets" to be furnished to health care professionals or authorized vaccine administrators, as well as those to be furnished to recipients of the product, which are described in section E of the "Emergency Use Authorization of Medical Products and Related Authorities" guidance (Ref. 3) and typically are part of pre-EUA discussions; and plans for providing such information in an emergency;
7. Information regarding the supply chain, which will help FDA to assess anticipated availability of the vaccine for its intended recipients and whether anticipated storage and distribution conditions will affect the vaccine's safety and effectiveness, including the following details:
 - Whether the product will be supplied to the U.S. Government or Vendor Managed Inventory (VMI)
 - Anticipated quantity of finished product on hand and the surge capabilities of the manufacturing site(s)
 - Details of the distributor(s) for the vaccine and plans for distribution.

B Chemistry, Manufacturing, and Controls

The EUA request should include information on chemistry, manufacturing, and controls; a list of each site where the product, if authorized, is or would be manufactured, relevant information about each site, and the current status of the manufacturing site(s) with respect to current good manufacturing practice (CGMP) requirements (Refs. 4, 5).

As noted above, in order to facilitate a complete and timely review of an EUA request, FDA expects that a detailed description of the manufacturing process and controls will be provided in a relevant IND or cross-referenced MF(s) as it becomes available but not less than one month prior to submission of an EUA request. Any manufacturing and process control data that will not be available at the time of submission of an EUA request should be discussed with FDA well in advance of the submission of the EUA request and identified in the submission.

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Following notice by a sponsor of intent to submit an EUA request as noted above, FDA will continue to work with the sponsor regarding resolution of any necessary manufacturing site issues resulting from a site visit or other information submitted. FDA will assess CGMP compliance for each manufacturing site using all available tools and information.

1. Manufacturing

Sufficient data should be submitted to support drug substance (DS) and drug product (DP) manufacturing to ensure the quality and consistency of the vaccine product that is produced. FDA generally expects a minimum of three Process Performance Qualification (PPQ) lots per manufacturing facility to support the consistency of vaccine quality. In addition, critical process parameters and in-process controls of specific unit operations should be qualified/validated. Evidence should be provided that all DS and DP manufacturing sites, including testing sites, are adequately qualified/validated to ensure that the equipment/process meets all predetermined specifications/intended purposes, and the production process is controlled and operates with quality oversight consistent with CGMP requirements. If more than one manufacturing facility is used to produce DS and DP, data should be provided to support the consistency of vaccine quality between manufacturing sites.

2. Control of Drug Substance and Drug Product

Product data as described below should be provided to support FDA's determination regarding the safety and effectiveness of the vaccine:

- a. Documentation establishing that critical source materials used in manufacturing are adequately controlled, including history and qualification of cell banks and virus banks, identification of all animal-derived materials used for cell culture and virus growth, and DP excipients.
- b. An evaluation and mitigation plan for potential adventitious agents.
- c. Data to demonstrate that the DS is sufficiently characterized in order to identify and understand the critical properties that impact performance and stability.
- d. A detailed description of the quality control system for all stages of manufacturing, including the testing program for in-process/intermediate product quality and DS and DP quality for release.
- e. Analytical methods and qualification/validation data for all quality-indicating assays. Validation data for assays used to evaluate critical vaccine qualities such as purity, identity, and potency are expected.
- f. The DS and DP development history and manufacturing changes introduced in Phase 1, 2, 3 and EUA lots, including analytical comparability of DS lots with these changes. Quality release data and supplementary characterization tests to assess the impact of the changes on the DS quality attributes should be provided.

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- g. A tabular listing of all clinical studies and DP lot numbers used in each study including DS lot genealogy, manufacturing processes used, and the manufacturing site, as well as the Certificates of Analysis (CoAs) for all clinical lots used in clinical studies and information on any lots that were initiated but not accepted for release.
- h. A stability plan including safety and stability-indicating tests and available stability data from all developmental, clinical, and commercial lots. Data to support short-term stability, reflecting storage conditions during transport and distribution and in clinics and covering the time from dose preparation to administration expected.
- i. Appropriate quality specifications should be established for all DP lots used under EUA and testing results for the final vaccine lots should be submitted to the IND at the time of product distribution.
- j. Aseptic-process information, including the appropriate validation studies.
- k. A description of sterile filtration and sterilization processes, as well as validation studies. Depyrogenation of container-closure systems, if applicable, should also be provided.
- l. Storage conditions, including the container-closure integrity, should be validated and this information should be provided.

3. Facilities

- a. Facility information should be submitted to demonstrate that the facilities are of suitable size and adequately designed to prevent contamination, cross-contamination, and mix-ups.
- b. Utility information, including validation information, should be provided for all utilities. For the heating, ventilation, and air conditioning (HVAC) system, it is important to demonstrate control by including area classifications, pressure differentials, and containment features where needed.
- c. Manufacturing equipment should be qualified, and a list of critical equipment for DS and DP should be submitted.
- d. Facility and equipment cleaning should be validated, and the validation should be submitted for review.
- e. A quality control unit should be established and have the responsibility for oversight of manufacturing, and review and release of components, containers and closures, labeling, in-process material, and final products. The quality control unit should have the responsibility for approving validation protocols and reports, investigating deviations, and instituting corrective and preventive actions.

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C. Safety and Effectiveness Information

The EUA request should include the following safety and effectiveness information, which will inform FDA’s determination regarding the product’s benefit-risk profile:

1. Bioassays for assessment of clinical endpoints

The diagnostic bioassays that were used to assess study endpoints of clinical studies supportive of the EUA request should be identified. FDA expects that the standard operating procedures (SOPs) and validation reports for the final assay methods, and a list of all laboratories where the clinical samples have been tested, will be submitted to support the EUA request.

2. Nonclinical:

- a. A list of the nonclinical studies conducted to support vaccine effectiveness and safety (e.g., characterization of markers associated with enhanced disease, biodistribution, shedding, and attenuation) should be provided, along with the timelines for study completion and submission of final study reports for all ongoing nonclinical studies as applicable.
- b. A final study report, if available, for a Developmental and Reproductive Toxicology (DART) study, or the timeline for study completion and submission of the final study report, should be provided in order to inform potential emergency use of the vaccine in pregnant women.

3. Clinical

- a. FDA acknowledges the potential to request an EUA for a COVID-19 vaccine based on an interim analysis of a clinical endpoint from a Phase 3 efficacy study. Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine’s benefits and risks and support issuance of an EUA would include not only meeting the prespecified success criteria for the study’s primary efficacy endpoint as described in the guidance for industry entitled “Development and Licensure of Vaccines to Prevent COVID-19” (Ref. 1) (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%), but also additional safety and effectiveness data as described below in this section. The timing of interim analyses planned for a Phase 3 study would thus ideally be aligned with the ability of the analyses to meet these criteria.
- b. An EUA request for a COVID-19 vaccine should include all safety data accumulated from Phase 1 and 2 studies conducted with the vaccine, with focus on serious adverse events (SAEs), adverse events of special interest, and cases of severe COVID-19 among study subjects. We recognize that the Phase 1 and 2

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safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request. The Phase 1 and 2 data are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

- c. Data from Phase 3 studies should include a median follow-up duration of at least two months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile, including: adverse events; cases of severe COVID-19 disease among study subjects; and cases of COVID-19 occurring during the timeframe when adaptive (rather than innate) and memory immune responses to the vaccine would be responsible for a protective effect.

In addition, FDA does not expect to be able to make a favorable benefit-risk determination that would support an EUA without Phase 3 data that include the following, which will help the Agency to assess the safety of the vaccine:

- i. Local and systemic solicited adverse reactions collected for the protocol-defined duration of follow-up in an adequate number of subjects to characterize reactogenicity in each protocol-defined age cohort participating in the trial;
 - ii. All safety data collected up to the point at which the database is locked to prepare the submission of the EUA request, including a high proportion of enrolled subjects (numbering well over 3,000 vaccine recipients) followed for SAEs and adverse events of special interest for at least one month after completion of the full vaccination regimen;⁷ and
 - iii. Sufficient cases of severe COVID-19 among study subjects to support low risk for vaccine-induced ERD (a total of 5 or more severe COVID-19 cases in the placebo group would generally be sufficient to assess whether the severe COVID-19 case split between vaccine vs. placebo groups supports a favorable benefit-risk profile or conversely raises a concern about ERD).
- d. Vaccine safety and COVID-19 outcomes in individuals with prior SARS-CoV-2 infection, who might have been asymptomatic, are important to examine because screening for prior infection is unlikely to occur prior to administration of COVID-19 vaccines under EUA. An EUA request should therefore include subgroup analyses of safety and efficacy endpoints stratified by prior infection status at study entry, as determined by pre-vaccination serology or medical history.

⁷ As noted in FDA's guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (Ref. 1), the pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure. FDA anticipates that adequately powered efficacy trials for COVID-19 vaccines will be of sufficient size to provide an acceptable safety database for each of the younger adult and elderly populations, provided that no significant safety concerns arise during clinical development that would warrant further evaluation.

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- e. The EUA request should include a plan for active follow-up for safety (including deaths and hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

VII. CONSIDERATIONS FOR CONTINUING CLINICAL TRIALS FOLLOWING ISSUANCE OF AN EUA FOR A COVID-19 VACCINE

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for stopping blinded follow-up in an ongoing clinical trial. An EUA request should include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated ERD as well as decreased effectiveness as immunity wanes over time) in sufficient numbers of subjects to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

VIII. CONSIDERATION OF AN EUA FOR A COVID-19 VACCINE BY AN FDA ADVISORY COMMITTEE

FDA expects to convene an open session of FDA's VRBPAC prior to the issuance of any EUA for a COVID-19 vaccine, to discuss whether the available safety and effectiveness data support authorization of an EUA for the specific request under review. This discussion, which will be specific to the particular vaccine that is the subject of the EUA request, will be separate from, and in addition to, any general discussion by the VRBPAC regarding the development, authorization, and/or licensure of vaccines to prevent COVID-19. A VRBPAC meeting may also include a closed session, if it is deemed necessary, to discuss proprietary CMC issues.

FDA expects to convene the VRBPAC for consideration of an EUA request for a COVID-19 vaccine that, on its face, contains the information required under section 564 of the FD&C Act (21 U.S.C. 360bbb-3) and includes the recommended data and information described above. FDA intends to provide briefing materials to the VRBPAC members as far in advance of any scheduled meeting as practicable and intends to post a publicly available version of the briefing materials on the FDA webpage no later than two full business days before the day the advisory committee meeting is scheduled to occur.

To facilitate discussion by the VRBPAC, an EUA request should be accompanied by briefing materials summarizing data to support the safety and effectiveness of the vaccine to be considered at the open session of the VRBPAC, and if requested by FDA, separate briefing materials related to manufacturing of the vaccine for a closed session. The purpose of any closed session would be limited to the review and discussion of manufacturing information that is considered confidential commercial or trade secret information exempt from public disclosure.

Timely consideration of the EUA request by the VRBPAC would be further facilitated by submission of briefing materials for the open session that the sponsor states are fully releasable. For additional information regarding the process for preparation and review of briefing materials for open FDA

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advisory committee meetings, sponsors should consult the guidance for industry entitled “Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members” (Ref. 6), although the time frames set forth in the appendix of that guidance may not be applicable to a meeting of the VRBPAC for a COVID-19 vaccine. Please see Appendix 1 for more information regarding submission of information in preparation for a VRBPAC meeting to consider a request for an EUA for a COVID-19 vaccine.

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APPENDIX 1: SUBMISSION OF INFORMATION IN PREPARATION FOR A VRBPAC MEETING

A Preparation and submission of briefing materials for the Advisory Committee meeting

For an open session of the VRBPAC, please plan to submit final and fully releasable briefing materials at the time of submission of an EUA request for a COVID-19 vaccine.

As noted in section VIII of this guidance, for certain EUA requests, FDA may determine that a closed session of the VRBPAC to discuss proprietary CMC information would be appropriate. In such circumstances, sponsors would not be expected to submit fully releasable briefing materials and should consult with OVRP regarding the submission of briefing materials for the closed session.

B Process

Final sponsor-prepared and FDA-prepared briefing documents will be made available to the public no later than two full business days prior to the meeting date on the FDA webpage under the respective Advisory Committee Meeting.

Publications need not be submitted with the briefing materials. If you choose to submit publications, the electronic submission should contain your actual briefing materials in one file and the publications in a separate file. The briefing materials should include a references section that lists these publications. Only the briefing materials will be posted on the FDA webpage; the file of publications will be sent to the committee members but will not be posted.

In addition to the fully releasable briefing materials, to facilitate timely consideration of the EUA request by the VRBPAC, the following additional information should be provided by the sponsor at the time of submission of the EUA request:

1. Point of Contact for Advisory Committee Related Matters

At the time of submission of the EUA request, please provide primary and alternative points of contact's name, title, address, e-mail address and phone numbers.

2. List of Investigators

At the time of submission of the EUA request, please provide as a searchable electronic copy, a list of investigators, and the clinical sites for all clinical trials supporting the submission(s) under review.

3. Meeting Participants

At the time of submission of the EUA request, please provide a list of all presenters and responders who will be representing you at the meeting, along with their affiliation(s).

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Representational activities include presenting, responding to questions, and/or sitting in the Sponsor/Industry section at the meeting.

Please note that there are restrictions for any current or former advisory committee members, or other past or present Special Government Employees (SGEs), to attend the meeting representing the sponsors before the Agency (5 CFR Part 2635).

The goal is to avoid situations in which a current or former advisory committee member and/or consultant might inadvertently violate the law concerning representational activities. It is a violation of ethics statute 18 U.S.C. 208 for a Federal Employee (including but not limited to full-time and part-time employees of the National Institutes of Health, Centers for Disease Control and Prevention, Department of Defense, and Veterans Affairs) to represent a third party before another Agency. Please note that Federal Employees will not be permitted to represent your company at the meeting.

4. Meeting Day Presentation Materials (slides)

It is recommended that your planned speakers' slides be numbered for ease of reference during the meeting by the committee members. Please provide us with an electronic version of the slide presentation five business days prior to the Advisory Committee meeting. If back-up slides are presented, we ask that you provide the backup slides in the same file as your core presentation. All slides will be also posted on FDA's webpage. Therefore, they must meet the requirements of section 508 of the Rehabilitation Act.⁸

⁸ Section 508 of the Rehabilitation Act of 1973 (29 U.S.C. 794(d)). *See also* Requirements Checklists for Section 508, available at <https://www.fda.gov/about-fda/internet-accessibility/requirements-checklists-section-508>.

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APPENDIX 2: EVALUATION OF VACCINES TO ADDRESS EMERGING SARS-COV-2 VARIANTS

A Background

In the U.S. there are currently two licensed COVID-19 vaccines (Comirnaty (COVID-19 Vaccine, mRNA) and Spikevax (COVID-19 Vaccine, mRNA)); three COVID-19 vaccines are currently authorized for emergency use (Janssen COVID-19 Vaccine, Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine). Additionally, numerous COVID-19 vaccines are in development in the U.S. and globally, many in advanced clinical trials. The U.S.-licensed and authorized vaccines and many investigational COVID-19 vaccines are designed to elicit a protective immune response to the SARS-CoV-2 Spike (S) protein, the major structural protein of the virus that has an essential role in attachment and infection of host cells. Several COVID-19 vaccines (e.g., mRNA vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be effective in clinical studies (Refs. 7-8). Evidence has accumulated from laboratory studies, pre-clinical animal studies, and clinical studies that indicates a neutralizing antibody response, primarily directed to the S protein, makes an important contribution to the protective response elicited by COVID-19 vaccines based on S protein antigens. Nevertheless, the relative contribution of neutralizing antibody to protection elicited by current vaccines is not defined, and it is likely that the role of neutralizing antibody in protection may differ depending on the type of vaccine. Further, the level of neutralizing antibody that reliably predicts protection has not been established.

Like most RNA viruses, SARS-CoV-2 is constantly evolving, and new variants have emerged that improve virus fitness for transmission. SARS-CoV-2 variants that include mutations in the S protein were identified within a few months after the start of the pandemic.

Understanding the potential risk of SARS-CoV-2 variants to those previously unexposed to the virus, to previously infected individuals, and to recent vaccinees, is an area of intense research focus. The emergence of SARS-CoV-2 variants with multiple mutations in the S protein (e.g., Alpha (B.1.1.7 lineage), Delta (B.1.617.2 and AY lineages) and Omicron (B.1.1.529 and BA lineages)) have raised concerns because of their increased transmission rates and because of evidence that current COVID-19 vaccines (herein referred to as prototype vaccines) licensed or authorized under EUA or otherwise in clinical development provide reduced protection against these variants (Refs. 9-11), at least with respect to mild disease (Refs. 12-14). With the expectation that new SARS-CoV-2 variants will continue to emerge over time, available COVID-19 vaccines may need to be modified to adequately protect against disease caused by these variants.

B Introduction

The following describes FDA's current thinking regarding the CMC, nonclinical data, and clinical data needed to support an amendment to an EUA under section 564 of the FD&C Act (21 U.S.C. 360bbb-3) for a vaccine for the prevention of COVID-19. These recommendations pertain to modified COVID-19 vaccines for the prevention of COVID-19, where the vaccine is made by the same process and manufacturer as an authorized or approved prototype vaccine but is modified in order to enhance efficacy against COVID-19

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caused by a SARS-CoV-2 variant(s). It should be recognized that FDA's thinking regarding data needed to authorize a modified COVID-19 vaccine may evolve as additional information is accrued with SARS-CoV-2 variants and corresponding vaccines.

Of note, the recommendations detailed below are specifically for pandemic COVID-19 vaccines that express the S protein and are made under the assumptions that neutralizing antibody to SARS-CoV-2 S is a major component of the vaccine protective response (or for a given vaccine construct, is likely to vary in proportion to the protective response), that an immune marker predictive of protection has not been established, and that it is not feasible to conduct clinical disease endpoint efficacy studies rapidly enough to respond to the emergence of SARS-CoV-2 variants that may escape immunity conferred by prototype vaccines. Assuming the prototype vaccine has been authorized under an EUA or is approved, it is expected that the modified COVID-19 vaccine against a SARS-CoV-2 variant made by the same manufacturer and process as the prototype COVID-19 vaccine would be authorized through an EUA amendment to the EUA for the prototype COVID-19 vaccine.

This Appendix does not address how it will be determined that a vaccine based on a new viral sequence is needed, determining which protein sequences should be expressed by such a vaccine, or approaches to follow-up of modified vaccines to ensure that they retain adequate effectiveness, and do not lose efficacy due to evolution of new viral variants. This document also does not address considerations for multivalent COVID-19 vaccines.

Other issues that FDA continues to consider, but are not discussed in this Appendix, include, and are not limited to:

- data indicating the need for a modified vaccine,
- what entity evaluates, decides and recommends whether a modified vaccine is needed, and
- the role of FDA's VRBPAC in determining the need for a modified vaccine in the U.S.

A request for an EUA amendment for the modified vaccine should address the following:

1. Chemistry, Manufacturing, and Controls

The EUA amendment should include information on CMC; a list of each site where the modified product, if authorized, is or would be manufactured, relevant information about each site and the current status of the manufacturing site(s) with respect to CGMP requirements.

FDA expects that much of the manufacturing process and controls, as well as the facilities for vaccine production, for the modified COVID-19 vaccine will be identical to that of the prototype COVID-19 vaccine. However, updated CMC data will need to be generated for the modified COVID-19 vaccine, as a scientific matter. The CMC data to support the modified vaccine formulation may differ depending on the vaccine platform, but at a minimum should include critical aspects of product characterization, a potency assay, and data on stability generated using the modified COVID-19 vaccine. Any changes made to the manufacturing process and process control should be discussed with FDA in advance of the EUA amendment submission.

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2. Nonclinical

A list of the nonclinical studies conducted to support vaccine effectiveness and safety (e.g., characterization of markers associated with enhanced disease, biodistribution, shedding, and attenuation) obtained with the prototype COVID-19 vaccine made by the same manufacturer and process should be provided.

In general, for a modified COVID-19 vaccine directed against a SARS-CoV-2 variant and made by the same manufacturer and process, conducting additional repeat dose toxicity studies or DART studies may not be warranted. Data from the vaccine platform or from the prototype vaccine will be considered in making this decision.

Data from studies in a relevant animal model receiving the prototype COVID-19 vaccine and the modified COVID-19 vaccine directed against SARS-CoV-2 variant(s) and subsequently challenged with wild-type viruses representing clinically relevant circulating variants, including the variant(s) of interest, are encouraged as they contribute to the totality of the evidence supporting the authorization of a modified COVID-19 vaccine. Vaccine manufacturers may submit the draft protocols for such studies to FDA. It should be recognized that conduct of challenge studies with any live SARS-CoV-2 requires a BSL-3 containment facility. These challenge/protection studies may be performed in parallel with the clinical immunogenicity studies described below.

3. Clinical data

a. Clinical data to support effectiveness of a modified vaccine

The effectiveness of a modified COVID-19 vaccine against a particular SARS-CoV-2 variant of concern (VOC) can be evaluated based on:

- The efficacy of primary vaccination with the manufacturer's authorized or approved prototype COVID-19 vaccine made by the same process and for which a clinical disease endpoint efficacy study has been conducted that met FDA pre-specified success criteria, AND
- Comparison of immune responses (assessed by neutralizing antibody) induced by the modified vaccine and the prototype vaccine.

The immunogenicity studies to assess the effectiveness of a modified COVID-19 vaccine against a particular VOC administered as primary vaccination, a first booster dose and a second booster dose are described below in this section (Appendix 2 B.3.a.). Each of these studies is described as having a contemporaneous comparator group who receive the prototype vaccine; however, serum samples from study subjects administered the prototype vaccine in a previously conducted study, if available, may be used in lieu of a contemporaneous comparator group if evaluated using the same assay(s) and provided that the prototype vaccine and modified vaccine groups are well-balanced with respect to factors that may affect interpretation of the immune response. Ideally, the modified vaccine would be evaluated in subjects spanning the age range for the authorized use of the prototype vaccine for primary and booster vaccination. If a more limited age range is studied it may, in certain situations, be reasonable to extrapolate the data to other age groups for which the

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prototype is authorized or approved. We acknowledge that certain aspects of the immunogenicity evaluations outlined below in this section (Appendix 2 B.3.a.) may be challenging, and in situations where available data support that certain studies or analyses would be infeasible, we would consider alternative approaches with appropriate justification. The assessment of effectiveness of a modified COVID-19 vaccine will take into account the totality of the immunogenicity data from the primary, secondary and descriptive analyses.

Primary Vaccination: Sponsors should conduct an immunogenicity study in which previously unvaccinated persons are randomized to receive either the modified COVID-19 vaccine or the prototype COVID-19 vaccine. The modified vaccine dose and dosing regimen should be the same as authorized (or approved) for the prototype vaccine. If high SARS-CoV-2 seroprevalence precludes conducting studies in a SARS-CoV-2 naïve population, the prototype vaccine and modified vaccine groups should ideally be well balanced with respect to SARS-CoV-2 infection history based on baseline serostatus (presence of nucleocapsid antibody) and/or laboratory confirmed COVID-19, and with respect to neutralizing antibody titer prior to vaccination. Subgroup analyses should be conducted to evaluate immunogenicity based on these variables.

Immune response comparisons and analyses to demonstrate effectiveness of a modified COVID-19 vaccine administered for primary vaccination are outlined below and in Table 1.

Primary immunogenicity analyses: The primary analysis should be a comparison of Geometric Mean Titer (GMT) against the particular VOC, elicited by the modified and prototype vaccine. The study should be designed and adequately powered to demonstrate statistical superiority of the GMT elicited by the modified vaccine as compared to the prototype vaccine. Ideally, the primary analysis would test for “super” superiority (margin of >1.5-fold for GMT ratio) to statistically exclude non-inferiority of the prototype vaccine compared with the modified vaccine. However, it would be acceptable to test for “simple” superiority (margin of >1-fold for GMT ratio) in the primary analysis and to test for “super” superiority as a secondary immunogenicity analysis.

A second co-primary analysis should be a comparison of seroresponse rates against the particular VOC, elicited by the modified and prototype vaccine. The study should be designed and adequately powered to demonstrate non-inferiority of the seroresponse rate elicited by the modified vaccine as compared to the prototype vaccine, using a non-inferiority margin of <5% for seroresponse rate difference. Alternatively, the co-primary analysis of seroresponse rates could test for superiority (“simple” superiority margin of >0% or “super” superiority margin of >10% for seroresponse rate difference). If the co-primary analysis of seroresponse rates will test for non-inferiority, FDA would expect that additional descriptive analyses of seroresponses against clinically relevant variants, including the particular VOC, support the benefit of the modified vaccine over the prototype vaccine. Determination of an appropriate seroresponse definition should be based on available data.

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Additional immunogenicity analyses: A secondary analysis should evaluate non-inferiority of seroresponse rates and GMTs against the particular VOC that are induced by the modified vaccine relative to seroresponse rates and GMTs against the virus upon which the prototype was based that are induced by the prototype vaccine. Non-inferiority margins should be 10% for seroresponse rates and 1.5-fold for GMTs, respectively. Alternate non-inferiority margins may be considered, with adequate justifications, on a case-by-case basis. Additional descriptive analyses should compare the seroresponse rates and GMTs in each group against other clinically relevant VOCs (e.g., currently or recently circulating variants) and against the virus upon which the prototype was based.

Table 1: Immune Response Comparisons and Analyses to Demonstrate Effectiveness of a Modified COVID-19 Vaccine Administered for Primary Vaccination

Immune response analyses	Modified Vaccine Group	Prototype Vaccine Group
Primary: Superiority*	GMT _V	GMT _V
Primary: Non-inferiority**	SRR _V	SRR _V
Secondary: Non-inferiority	IR _V	IR _O
Secondary: “Super” Superiority (if not primary)	IR _V	IR _V
Additional Descriptive	IR _O	IR _O
Additional Descriptive	IR _{R-V}	IR _{R-V}

*Ideally the primary analyses will test for “super” superiority (margin of >1.5-fold for GMT ratio). However, it would be acceptable to test for “simple” superiority (margin of >1-fold for GMT ratio) in the primary analysis and to test for “super” superiority as a secondary immunogenicity analysis.

**Non-Inferiority margin of <5% for SRR difference. Alternatively, the co-primary analysis of SRR could test for superiority (“simple” superiority margin of >0% or “super” superiority margin of >10% for SRR difference).

GMT_V = GMT against the particular VOC targeted by the modified vaccine

SRR_V = Seroresponse rate against the particular VOC targeted by the modified vaccine

IR_V = seroresponse rate and GMT against the particular VOC targeted by the modified vaccine

IR_O = seroresponse rate and GMT against the virus upon which the prototype is based

IR_{R-V} = seroresponse rate and GMT against other clinically relevant VOCs

First Booster Dose: Sponsors should conduct an immunogenicity study in which persons who have previously completed primary vaccination with the prototype

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COVID-19 vaccine, administered according to the authorized (or approved) dose and dosing regimen, are randomized to receive a booster dose of either the modified COVID-19 vaccine or the prototype COVID-19 vaccine. Alternate study designs can be considered, for example a study in which subjects who have completed primary vaccination with other authorized (or approved) prototype vaccines are randomized to receive a booster dose with either the prototype vaccine or the modified vaccine. If the study population is heterogeneous with respect to previous vaccines received, the design should take into consideration factors that may affect interpretation of the immune response to the booster dose (i.e., the prototype vaccine and modified vaccine groups should ideally be well balanced with respect to vaccination history and SARS-CoV-2 infection history based on baseline serostatus (presence of nucleocapsid antibody), laboratory confirmed COVID-19, and neutralizing antibody titer prior to the booster dose). Subgroup analyses should be conducted to evaluate immunogenicity based on these variables.

Immune response comparisons and analyses to demonstrate effectiveness of a modified COVID-19 vaccine administered as a first booster dose are outlined below and in Table 2.

Primary immunogenicity analyses: The primary analysis should be a comparison of GMTs against the particular VOC, elicited by the modified and prototype vaccine. The study should be designed and adequately powered to demonstrate statistical superiority of the GMT elicited by the modified vaccine as compared to the prototype vaccine. Ideally, the primary analysis would test for “super” superiority (margin of >1.5-fold for GMT ratio) to statistically exclude non-inferiority of the prototype vaccine compared with the modified vaccine. However, it would be acceptable to test for “simple” superiority (margin of >1-fold for GMT ratio) in the primary analysis and to test for “super” superiority as a secondary immunogenicity analysis.

A second co-primary analysis should be a comparison of seroresponse rates against the particular VOC, elicited by the modified and prototype vaccine. The study should be designed and adequately powered to demonstrate non-inferiority of the seroresponse rate elicited by the modified vaccine as compared to the prototype vaccine, using a non-inferiority margin of <5% for seroresponse rate difference. Alternatively, the co-primary analysis of seroresponse rates could test for superiority (“simple” superiority margin of >0% or “super” superiority margin of >10% for seroresponse rate difference). If the co-primary analysis of seroresponse rates will test for non-inferiority, FDA would expect that additional descriptive analyses of seroresponses against clinically relevant variants, including the particular VOC, support the benefit of the modified vaccine over the prototype vaccine. Determination of an appropriate seroresponse definition for a first booster dose should be based on available data.

Additional immunogenicity analyses: The following descriptive analyses should be conducted:

- Comparison of the seroresponse rates and GMTs following the booster dose in each group against the virus upon which the prototype was based.

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- Comparison of the seroresponse rates and GMTs following the booster dose in each group against other clinically relevant VOCs (e.g., currently or recently circulating variants).
- Comparison of the immune response elicited by a booster dose of the modified vaccine against the particular VOC to that elicited following primary vaccination with the prototype vaccine against the virus upon which the prototype was based.
- Comparison of the immune response elicited by a booster dose of the modified vaccine to that elicited following primary vaccination with the prototype vaccine against the virus upon which the prototype was based.
- Comparison of the immune response elicited by a booster dose of the modified vaccine to that elicited following primary vaccination with the prototype vaccine against other clinically relevant VOCs.

The descriptive comparisons to the immune response after primary vaccination may be limited to a comparison of GMTs.

Table 2: Immune Response Comparisons and Analyses to Demonstrate Effectiveness of a Modified COVID-19 Vaccine Administered as a First Booster Dose

Immune response analyses	Modified Booster Vaccine Group	Prototype Booster Vaccine Group	Prototype Primary Vaccination Vaccine Group*
Co-Primary: Superiority**	GMT _V	GMT _V	NA
Co-Primary: Non-inferiority***	SRR _V	SRR _V	NA
Secondary: “Super” Superiority (if not primary)	GMT _V	GMT _V	NA
Additional Descriptive	IR _O	IR _O	NA
Additional Descriptive	IR _{R-V}	IR _{R-V}	NA
Additional Descriptive	IR _V	NA	IR _O
Additional Descriptive	IR _O	NA	IR _O
Additional Descriptive	IR _{R-V}	NA	IR _{R-V}

*Comparisons to the immune response following primary vaccination may be comparisons to sera obtained in different studies and may be limited to GMTs.

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**Ideally the primary analysis of GMTs will test for “super” superiority (margin of >1.5-fold for GMT ratio). However, it would be acceptable to test for “simple” superiority (margin of >1-fold for GMT ratio) in the primary analyses and to test for “super” superiority as secondary analysis of GMT.
***Non-Inferiority margin of <5% for SRR difference. Alternatively, the co-primary analysis of SRR could test for superiority (“simple” superiority margin of >0% or “super” superiority margin of >10% for SRR difference).

NA = Not Applicable

GMT_V = GMT against the particular VOC targeted by the modified vaccine

SRR_V = Seroresponse rate against the particular VOC targeted by the modified vaccine

IR_V = seroresponse rates and GMT against the particular VOC targeted by the modified vaccine

IR_O = seroresponse rates and GMT against the virus upon which the prototype is based

IR_{R-V} = seroresponse rates and GMT against other clinically relevant VOCs

Second booster dose: Sponsors should conduct an immunogenicity study in which persons who have completed primary and first booster vaccination with the prototype COVID-19 vaccine, administered according to the authorized or approved (primary vaccination) and authorized (booster vaccination) dose and dosing regimen, are randomized to receive a second booster dose of either the modified COVID-19 vaccine or the prototype COVID-19 vaccine. Alternate study designs can be considered, for example a study in which subjects who have completed primary vaccination and first booster with any combination of authorized or approved (primary vaccination) and authorized (booster vaccination) prototype vaccines are randomized to receive a second booster dose with either the prototype vaccine or the modified vaccine. If the study population is heterogeneous with respect to previous vaccines received, the design should take into consideration factors that may affect interpretation of the immune response to the second booster dose (i.e., the prototype vaccine and modified vaccine groups should ideally be well balanced with respect to vaccination history and SARS-CoV-2 infection history based on baseline serostatus (presence of nucleocapsid antibody), laboratory confirmed COVID-19, and neutralizing antibody titer prior to the second booster dose). Subgroup analyses should be conducted to evaluate immunogenicity based on these variables.

Immune response comparisons and analyses to demonstrate effectiveness of a modified COVID-19 vaccine administered as a second booster dose are outlined below and in Table 3.

Primary immunogenicity analyses: One co-primary analysis should be a comparison of GMTs against the particular VOC, elicited by the modified and prototype vaccine. The study should be designed and adequately powered to demonstrate statistical superiority of the GMT elicited by the modified vaccine as compared to the prototype vaccine. Ideally, the primary analysis would test for “super” superiority (margin of >1.5-fold for GMT ratio) to statistically exclude non-inferiority of the prototype vaccine compared with the modified vaccine. However, it would be acceptable to test for “simple” superiority (margin of >1-fold for GMT ratio) in the primary analyses and to test for “super” superiority as a secondary immunogenicity analysis.

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A second co-primary analysis should be a comparison of seroresponse rates against the particular VOC, elicited by the modified and prototype vaccine. The study should be designed and adequately powered to demonstrate non-inferiority of the seroresponse rate elicited by the modified vaccine as compared to the prototype vaccine, using a non-inferiority margin of <5% for seroresponse rate difference. Alternatively, the co-primary analysis of seroresponse rates could test for superiority (“simple” superiority margin of >0% or “super” superiority margin of >10% for seroresponse rate difference). If the coprimary analysis of seroresponse rates will test for non-inferiority, FDA would expect that additional descriptive analyses of seroresponses against clinically relevant variants, including the particular VOC, support the benefit of the variant vaccine over the prototype vaccine. Determination of an appropriate seroresponse definition for a second booster dose should be based on available data

Additional Immunogenicity Analyses: The following descriptive analyses should be conducted:

- Comparison of the seroresponse rates and GMTs following the second booster dose in each group against the virus upon which the prototype was based.
- Comparison of the seroresponse rates and GMTs following the second booster dose in each group against other clinically relevant VOCs (e.g., currently or recently circulating variants).
- Comparison of the immune response elicited by a second booster dose of the modified vaccine against to that elicited following a first booster dose with the prototype vaccine against the particular VOC.
- Comparison of the immune response elicited by a second booster dose of the modified vaccine to that elicited following a first booster dose with the prototype vaccine against the virus upon which the prototype was based.
- Comparison of the immune response elicited by a second booster dose of the modified vaccine to that elicited following a first booster dose with the prototype vaccine against other clinically relevant VOCs.

The descriptive comparisons to the immune response after the first booster dose may be limited to a comparison of GMTs.

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Table 3: Immune Response Comparisons and Analyses to Demonstrate Effectiveness of a Modified COVID-19 Vaccine Administered as a Second Booster Dose

Immune response analysis	Modified Booster #2 Vaccine Group	Prototype Booster #2 Vaccine Group	Prototype Booster #1 Vaccine Group*
Co-Primary: Superiority**	GMT _V	GMT _V	NA
Co-Primary: Non-inferiority***	SRR _V	SRR _V	NA
Secondary: “Super” Superiority (if not primary)	GMT _V	GMT _V	NA
Additional Descriptive	IR _O	IR _O	NA
Additional Descriptive	IR _{R-V}	IR _{R-V}	NA
Additional Descriptive	IR _V	NA	IR _V
Additional Descriptive	IR _O	NA	IR _O
Additional Descriptive	IR _{R-V}	NA	IR _{R-V}

*Comparisons to the immune response following the first booster dose may comparisons to sera obtained in different studies and may be limited to GMTs.

**Ideally the primary analyses will test for “super” superiority (margin of >1.5-fold for GMT ratio). However, it would be acceptable to test for “simple” superiority (margin of >1-fold for GMT ratio) in the primary analysis and to test for “super” superiority as a secondary immunogenicity analysis.

NA = Not Applicable

***Non-Inferiority margin of <5% for seroresponse rate difference. Alternatively, the co-primary analysis of SRR could test for superiority (“simple” superiority margin of >0% or “super” superiority margin of >10% for seroresponse rate difference).

GMT_V = geometric mean titer against the particular VOC targeted by the modified vaccine

SRR_V = seroresponse rate against the particular VOC targeted by the modified vaccine

IR_V = SRR and GMT against the particular VOC targeted by the modified vaccine

IR_O = SRR and GMT against the virus upon which the prototype is based

IR_{R-V} = SRR and GMT against other clinically relevant VOCs

b. Clinical data to support safety of a modified vaccine

Safety assessments, including solicited local and systemic adverse events assessed daily for at least 7 days after each study vaccination as well as serious and other

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unsolicited adverse events assessed during the immunogenicity evaluation period, may be sufficient to support EUA of the modified COVID-19 vaccine. However, evaluation of the modified COVID-19 vaccine in a larger safety database than initially planned for immunogenicity studies may be warranted if safety signals arise, and studies should also plan for longer-term assessments of serious and other medically attended adverse events.

Assays for assessment of immunogenicity endpoints

The assays used to assess immunogenicity endpoints of clinical studies should be identified. Even though an immune marker predictive of protection against COVID-19 has not been established to date, depending on the vaccine construct, neutralizing antibody may be considered a relevant measure of immunogenicity.

Data demonstrating the ability of the modified COVID-19 vaccine to induce a neutralizing antibody response are needed, as a scientific matter. These may be derived from virus neutralization assays (using pseudovirus or wildtype virus) assessing neutralization of SARS-CoV-2 viruses (including the virus from which the prototype vaccine was derived as well as variants of interest) with clinical serology samples obtained from persons immunized with the prototype and/or the modified COVID-19 vaccine construct.

FDA expects that the SOPs and validation reports for the final assay methods, and a list of all laboratories where the clinical samples have been tested, will be submitted to support the EUA amendment.

4. Additional considerations

Currently, it is not known whether the immunogenicity and safety profiles of vaccines against SARS-CoV-2 variants will be comparable to those of vaccines against the original SARS-CoV-2 virus and whether regular (e.g., annual) modifications will be needed. Thus, manufacturers should generate the data to support authorization of a modified COVID-19 vaccine as outlined above. Further discussions will be necessary to decide whether in the future, certain or all modified COVID-19 vaccines may be authorized without the need for clinical studies.

Developers are encouraged to perform exploratory studies regarding the ability of modified vaccines to boost immune responses to an appropriate level, even if the viral sequence being evaluated may not ultimately be selected for use in a modified vaccine. Such studies may provide important dose-finding and safety information.

If a manufacturer plans to develop a modified monovalent vaccine against a variant, it will be important to ensure that the modified vaccine can be clearly distinguished from vaccines made by the manufacturer that target the original virus.