

Emergency Use Authorization

Overview and Considerations for COVID-19 Vaccines

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Introduction

- The COVID-19 pandemic continues to worsen in the U.S. and world-wide
 - >16 million cases, >300,000 deaths in U.S. to date*
 - ~1.5 million cases, >17,000 deaths in U.S. in the week ending December 15*
- On December 11, 2020, FDA issued an Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine
 - For active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older
 - EUA issued after December 10, 2020 VRBPAC meeting to discuss the vaccine, data informing its benefits and risks, and plans for further evaluation

*Centers for Disease Control and Prevention, <https://covid.cdc.gov/covid-data-tracker/>

Introduction

- On November 30, 2020, Moderna Therapeutics submitted an EUA request for the Moderna COVID-19 vaccine (mRNA-1273)
 - mRNA/lipid nanoparticle vaccine administered as a 2 dose regimen, 28 days apart
 - Requested use is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older
 - Information submitted with the request includes safety and efficacy data from a large (N>30,000) randomized, blinded, placebo-controlled Phase 3 trial



Introduction

- FDA has been conducting a comprehensive review of the Moderna COVID-19 vaccine EUA submission received on November 30, 2020, including:
 - Verification of clinical data integrity and Moderna’s analyses, and additional FDA analyses, from datasets provided in the submission
 - Ongoing review of manufacturing, non-clinical, and clinical assay information
 - Review and revision of prescribing information and fact sheets for vaccine recipients and healthcare providers
 - Multiple information requests to Moderna to address questions and clarifications
 - Preparation for today’s VRBPAC meeting
- Today’s VRBPAC meeting continues FDA’s commitment to an expedited review process that is transparent, scientifically sound, and data-driven

EUA Legal Authority



- Established in Section 564 of the Federal Food, Drug, and Cosmetic Act
- Allows for FDA authorization of unapproved medical products (or unapproved uses of approved medical products) to address public health emergencies related to biological, chemical, radiological, or nuclear agents
- Requires prior determination of a threat, and declaration of circumstances justifying need for EUA to address that threat, by the Secretary of Homeland Security, Defense, or Health and Human Services
 - HHS Secretary Azar issued a declaration on March 27, 2020, justifying EUA of drugs and biological products to address the COVID-19 pandemic

Criteria for FDA Issuance of EUA

- The agent referred to in the EUA declaration can cause a serious or life-threatening disease or condition
- The medical product may be effective to prevent, diagnose, or treat the serious or life-threatening condition caused by the agent
- The known and potential benefits of the product outweigh the known and potential risks of the product
- No adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition
 - Only FDA-approved product for COVID-19 is remdesivir (for treatment, not prevention)
 - The Pfizer-BioNTech COVID-19 vaccine is available under EUA for prevention of COVID-19 but remains unapproved (and quantity available for mass vaccination is limited)

COVID-19 Vaccine EUA - FDA Expectations



- FDA expectations were discussed in detail at October 22, 2020, and December 10, 2020, VRBPAC meetings and described in FDA Guidance, [Emergency Use Authorization for Vaccines to Prevent COVID-19](#)
 - Data to demonstrate manufacturing quality and consistency
 - Clear and compelling safety and efficacy data to support favorable benefit-risk of the vaccine when rapidly deployed for administration to millions of individuals, including healthy people
 - Plans for further evaluation of vaccine safety and effectiveness, including in ongoing clinical trials, active and passive safety monitoring during use under EUA, and observational studies



Issuance of EUA for a COVID-19 Vaccine

- Will specify conditions of use for which benefit-risk has been determined to be favorable based on review of available data, including:
 - Population(s) to be included in the EUA
 - Conditions for vaccine distribution and administration
 - Requirements for safety monitoring and reporting of adverse events
- Will provide information to vaccine recipients and healthcare providers by way of prescribing information and fact sheets that describe:
 - The investigational nature of the product
 - The known and potential benefits and risks
 - Available alternatives and option to refuse vaccination



Issuance of EUA for a COVID-19 Vaccine

- EUA may be revised or revoked if:
 - Circumstances justifying the EUA no longer exist
 - Criteria for issuance are no longer met
 - Other circumstances arise that warrant changes necessary to protect public health or safety, e.g. based on new information concerning:
 - Vaccine safety or effectiveness
 - Vaccine manufacturing or quality
 - COVID-19 epidemiology or pathogenesis

VRBPAC Agenda



- Considerations for placebo-controlled trial design if an unlicensed vaccine becomes available (Steven Goodman)
- Sponsor presentation (Moderna)
- Open public hearing
- Lunch break
- FDA presentation of EUA review, discussion items, and question for vote
- Committee discussion and vote



Item for VRBPAC Discussion (no vote)

In considering Moderna's plans for unblinding and crossover of placebo recipients, please discuss the most critical data to further inform vaccine safety and effectiveness to support licensure that should be accrued in:

- Ongoing clinical trials with the Moderna COVID-19 vaccine
- Other studies (e.g., additional clinical trials or observational studies) with the Moderna COVID-19 vaccine



Question for VRBPAC Vote (yes/no)

Based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older?



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FDA Expectations for Clinical Data

- Efficacy data from at least one well-designed Phase 3 trial demonstrating protection against SARS-CoV-2 infection or disease:
 - Point estimate of least 50% vs. placebo comparator
 - Appropriately alpha-adjusted confidence interval lower bound >30%
- Safety data from throughout clinical development to evaluate reactogenicity, serious AEs, and AEs of special interest
 - Including a high proportion of Phase 3 study subjects followed for at least 1 month after completion of the full vaccination regimen
- Sufficient cases of severe COVID-19 to assess for signals of enhanced disease (and preliminary evidence of protection against severe disease)



FDA Expectations for Clinical Data

- A planned case-driven interim efficacy analysis and associated safety analyses could provide data to support an EUA
 - These analyses should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen
- Reasons for expectation of 2 months median follow-up:
 - Allows time for potential immune-mediated adverse reactions to be evaluated (uncommon but clinically significant immune-mediated adverse reactions to preventive vaccines generally have onset within 6 weeks following vaccination)
 - Ensures that vaccine efficacy is assessed during the time when adaptive/memory immune responses (rather than innate responses) are mediating protection
 - Allows for early assessment of waning protection and signals of enhanced disease

FDA Expectations for Further Evaluation

- Following issuance of an EUA, further vaccine evaluation would be needed:
 - For ongoing benefit/risk assessment to support continuation of the EUA
 - To accrue additional data to support licensure as soon as possible and/or to inform labeling
- Further vaccine evaluation following issuance of an EUA would include:
 - Longer-term follow-up for safety, including in larger numbers of vaccine recipients and in populations with lower representation in clinical trials
 - More precise estimation of vaccine effectiveness in specific populations
 - More robust assessment of effectiveness against aspects of SARS-CoV-2 infection or disease
 - Characterization of duration of protection
 - Investigation of immune biomarkers that might predict protection
 - Ongoing monitoring for signals of enhanced disease

FDA Expectations for Further Evaluation

- Issuance of an EUA for a COVID-19 vaccine would be contingent upon the ability to conduct further vaccine evaluation through a combination of:
 - Active follow-up of vaccine recipients under the EUA
 - Passive monitoring for clinically significant adverse reactions using established reporting mechanisms (e.g., VAERS)
 - Observational studies, including those that leverage healthcare claims databases
 - Continuation of blinded, placebo-controlled follow-up in ongoing clinical trials for as long as is feasible and strategies to handle loss of follow-up
- FDA does not consider issuance of an EUA for a COVID-19 vaccine to necessitate immediate unblinding of ongoing clinical trials or offering vaccine to all placebo recipients
 - Trial participants may choose to withdraw from follow-up for any reason, including to receive vaccine made available under EUA