U.S. FOOD & DRUG ADMINISTRATION

Emergency Use Authorization

Overview and Considerations for COVID-19 Vaccines

Doran Fink, MD, PhD

Deputy Director – Clinical, Division of Vaccines and Related Products Applications,

Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, FDA

December 10, 2020

Introduction

- The VRBPAC last convened on October 22, 2020, to discuss development, licensure, and emergency use authorization (EUA) of COVID-19 preventive vaccines
- Since the October 22, 2020, VRBPAC meeting, COVID-19 cases and associated hospitalizations and deaths have increased in the U.S. and world-wide
- On November 20, 2020, Pfizer submitted an EUA request for the Pfizer-BioNTech COVID-19 vaccine (BNT162b2)
  - mRNA/lipid nanoparticle vaccine administered as a 2 dose regimen, 21 days apart
  - Requested use is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older
  - Information submitted with the request includes safety and efficacy data from a large (N>43,000) randomized, blinded, placebo-controlled Phase 3 trial

Introduction

- FDA has been conducting a comprehensive review of the Pfizer-BioNTech COVID-19 vaccine EUA submission received on November 20, 2020, including:
  - Verification of clinical data integrity and Pfizer analyses, and additional FDA analyses, from datasets provided in the submission
  - Ongoing review of chemistry, manufacturing and control information, non-clinical data, and clinical assays, including information submitted shortly prior to the EUA request
  - Review and revision of prescribing information and fact sheets for vaccine recipients and healthcare providers
  - Multiple information requests to Pfizer 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)
  - Additional products have EUA but not FDA approval (none for prevention of COVID-19)

COVID-19 Vaccine EUA - FDA Expectations

- Discussed at October 22, 2020, VRBPAC meeting and 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

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

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

- Update on COVID-19 epidemiology (CDC)
- Plans for vaccine safety and effectiveness monitoring (CDC)
- Operational distribution plans (CDC)
- Considerations for placebo-controlled trial design if an unlicensed vaccine becomes available
- Open public hearing
- Sponsor presentation (Pfizer)
- FDA presentation and voting questions
- Committee discussion and vote

Items for VRBPAC Discussion (no vote)

1. Pfizer has proposed a plan for continuation of blinded, placebo-controlled follow-up in ongoing trials if the vaccine were made available under EUA. Please discuss Pfizer's plan, including how loss of blinded, placebo-controlled follow-up in ongoing trials should be addressed.

2. Please discuss any gaps in plans described today and in the briefing documents for further evaluation of vaccine safety and effectiveness in populations who receive the Pfizer-BioNTech Vaccine under an EUA.

Question for VRBPAC Vote (yes/no)

Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older?


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