Update from the Vaccines and Related Biologics Products Advisory Committee (VRBPAC) Meeting of October 22, 2020

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Introduction

- The Vaccines and Related Biological Products Advisory Committee (VRBPAC) reviews and evaluates data concerning the safety, effectiveness, and appropriate use of vaccines and related biological products
  - VRBPAC is a committee of experts external to FDA that provides input upon request by FDA on certain regulatory actions (e.g., licensure of new vaccines) and on more general topics critical to advancing regulatory science
  - VRBPAC recommendations are non-binding but usually followed by FDA
- The VRBPAC met on October 22, 2020, for a general discussion of the development, authorization and/or licensure of vaccines to prevent COVID-19
  - Open meeting with live webcast accessible to public
  - No discussion of specific COVID-19 vaccine candidates or vote on recommendations

VRBPAC Agenda – 10/22/20

- FDA introduction and presentation of discussion points
- Epidemiology, virology and clinical features of COVID-19 (CDC)
- NIH activities in the development of vaccines against COVID-19
- BARDA activities in the development of vaccines against COVID-19
- CDC plans for safety/effectiveness monitoring & evaluation during EUA use and post-licensure
- FDA surveillance systems and plans for post-marketing/post-authorization evaluation
- Operational aspects of COVID-19 vaccine distribution and tracking (CDC)
- COVID-19 vaccine confidence (Reagan-Udall Foundation)
- Licensure and emergency use authorization of vaccines to prevent COVID-19 – manufacturing and clinical considerations (FDA)
- Open Public Hearing
- Committee Discussion and Recommendations

FDA Presentations

- Described considerations for manufacturing and clinical information needed to support licensure or emergency use authorization (EUA) of COVID-19 vaccines, as described in recent FDA guidance
  - **Development and Licensure of Vaccines to Prevent COVID-19** (June 2020)
  - **Emergency Use Authorization for Vaccines to Prevent COVID-19** (October 2020)

- Expanded on and explained reasoning behind considerations outlined in the guidance documents
  - To provide reassurance that FDA will rely on sound science, established regulatory standards, and a transparent process for evaluating COVID-19 vaccine candidates

Clinical Considerations for EUA

- 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, following a planned interim analysis in an ongoing Phase 3 trial
- A favorable benefit/risk determination to support issuance of an EUA in this scenario would require, in addition to adequate manufacturing information:
  - Efficacy data showing protection against SARS-CoV-2 infection or disease with a point estimate of least 50% vs. placebo comparator and an appropriately alpha-adjusted confidence interval lower bound >30%
  - At least half of Phase 3 study subjects followed for both safety and efficacy for at least 2 months following completion of the full vaccination regimen
  - Safety data from throughout clinical development (including well over 3,000 Phase 3 vaccine recipients) to evaluate reactogenicity, serious AEs, and AEs of special interest
  - Sufficient cases of severe COVID-19 to assess for signals of enhanced disease

Clinical Considerations for EUA

- Reasons for a median follow-up of at least 2 months after completion of the full vaccination regimen to support issuance of an EUA for a COVID-19 vaccine:
  - 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 period when adaptive/memory immune responses (rather than innate responses) are mediating protection
  - Allows for early assessment of waning protection and signals of enhanced disease

Clinical Considerations for EUA

- Following a successful efficacy analysis that supports issuance of an EUA, further evaluation of a COVID-19 vaccine would be needed:
  - For ongoing benefit/risk assessments for continuation of the EUA
  - To accrue additional data to support licensure and/or to inform labeling
- Continued evaluation of a COVID-19 vaccine made available under 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
  - More robust assessment of effectiveness against specific 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

Clinical Considerations for EUA

- 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

Questions for VRBPAC Discussion

- Please discuss FDA's approach to safety and effectiveness data as outlined in the respective guidance documents
- Please discuss strategies for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine
- Please discuss studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
  - Further evaluate safety, effectiveness and immune markers of protection
  - Evaluate the safety and effectiveness in specific populations

VRBPAC Discussion

- VRBPAC expressed concerns about public vaccine confidence, consistent with those described in the Reagan-Udall Foundation presentation:
  - Hesitancy around acceptance and use of COVID-19 vaccines will continue to be driven by speed of vaccine development and perception of uncertainty and limitations of data
  - Issues with COVID-19 vaccine deployment could adversely impact public confidence in vaccines in general
  - Regulatory actions to make COVID-19 vaccines widely available therefore need to be transparent, effectively communicated, and above all supported by adequate data

VRBPAC Discussion

- Broad agreement that data to support issuance of an EUA for a COVID-19 vaccine should not be less than the standards outlined the October 2020 FDA guidance.
- Some VRBPAC members expressed concerns that:
  - A median follow-up of 2 months after completion of the vaccination regimen would not be sufficient to support an EUA for rapid and widespread deployment, in particular for vaccines manufactured using novel platforms
  - A successful interim efficacy analysis (with more limited COVID-19 cases and wider confidence intervals compared to a final analysis) would not be sufficient to support an EUA for rapid and widespread deployment
- Other VRBPAC members considered 2 months median follow-up sufficient to support issuance of an EUA
  - Evaluation for rare AEs and waning protection could best be accomplished by surveillance during use under EUA

VRBPAC Discussion

- Some VRBPAC members expressed concern about COVID-19 of any severity as the primary efficacy endpoint in current Phase 3 trials
  - Analyses to support licensure or EUA may provide limited information on severe disease
- FDA and some VRBPAC members discussed that primary endpoints were selected based on feasibility and prior experience with preventive vaccines
  - Vaccines are typically approved based on data showing prevention of laboratory-confirmed disease, regardless of severity
  - Experience supports that vaccine effectiveness increases with more specific (e.g., more severe) case definitions
  - Analyses to support EUA will include some information on severe disease, but insisting on adequately powered analyses of severe disease (which is lower incidence than less severe disease) could delay availability of an impactful vaccine

VRBPAC Discussion

- VRBPAC members expressed concern about clinical trial recruitment of (and accrual of data in) populations most affected by COVID-19, including:
  - Racial and ethnic minorities
  - Elderly individuals
  - Individuals with medical comorbidities
- FDA discussed that published guidance and advice to COVID-19 vaccine manufacturers has advocated for inclusion of these populations in trials
  - No regulatory mechanism for mandating trial recruitment
  - Demographic and medical history data from trial participants will be considered in regulatory decisions (e.g., age groups approved or authorized for use) and will be reflected in vaccine labeling to inform healthcare providers and vaccine recipients
  - Vaccine manufacturers have been publicizing enrollment demographics for their trials

VRBPAC Discussion

- Discussion around considerations for pediatric development and data to support use in pediatric populations
  - Need for safety assessments that include careful evaluation for immune-mediated reactions or enhanced disease (e.g., MIS-C/MIS-A) to support benefit/risk considerations for pediatric enrollment in clinical trials and for vaccine authorization or approval in pediatric age groups
  - Immunobridging approaches to infer vaccine effectiveness in pediatric populations will benefit from evolving understanding of natural and vaccine-elicited immunity
- Broad agreement that blinded, placebo-controlled follow-up in ongoing trials should continue for as long as is feasible, including after EUA
  - Concern expressed that if a COVID-19 vaccine were widely deployed under EUA based on limited data, could harm further accrual of critical data from placebo-controlled follow-up
  - Agreement with need for robust strategies for vaccine evaluation following licensure or EUA to complement (and replace once it becomes infeasible) placebo-controlled follow-up

VRBPAC Discussion

- Question raised about expanded access as an alternative to EUA
  - FDA explained that expanded access is another regulatory mechanism for making investigational products to address serious diseases available outside of clinical trials
- An expanded access treatment protocol could be considered to allow for deployment of a COVID-19 vaccine
  - Benefit/risk considerations would be similar to EUA and based on available data and proposed use (e.g., populations and numbers of individuals to be vaccinated)
  - Other considerations (including for planning and implementation) are different from EUA
  - Expanded access treatment protocol would be conducted under IND regulations, with requirements including (but not limited to) informed consent for clinical investigation, institutional review board oversight, and investigator responsibilities for vaccine providers

Next Steps

- FDA will consider October 22 VRBPAC feedback in continuing to balance:
  - Public health goal of safe and effective vaccines to address the COVID-19 pandemic
  - Obligation to ensure that authorization or approval of any COVID-19 vaccine complies with regulatory requirements for sufficient safety, effectiveness, and manufacturing information to support favorable benefit/risk for vaccine recipients
- The VRBPAC will be re-convened prior to any FDA action to approve or issue an EUA for a COVID-19 vaccine and will:
  - Evaluate and discuss data submitted in support of the licensure application/EUA request
  - Vote on recommendations as to whether the data support vaccine licensure/proposed use of the vaccine under EUA


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