LICENSURE AND EMERGENCY USE AUTHORIZATION OF VACCINES TO PREVENT COVID-19:
CLINICAL CONSIDERATIONS

Vaccines and Related Biological Products
Advisory Committee (10/22/2020)

Doran Fink, MD, PhD, Deputy Director – Clinical
Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review/CBER/FDA

Introduction

FDA

- **A worldwide effort is underway to develop safe and effective vaccines to address the COVID-19 pandemic as quickly as possible**

- **CBER is committed to ensuring that COVID-19 vaccines are safe and effective by relying on sound science, established regulatory standards, and transparent decision making in our review of COVID-19 vaccine candidates**

  – To ensure that any COVID-19 vaccine approved or authorized for widespread use will be safe and will have a meaningful impact

  – To ensure public trust and confidence in COVID-19 vaccines, and vaccines in general

Overview

FDA

- **Clinical data to support licensure of COVID-19 vaccines**

  - **FDA Guidance (June 2020):**

    Development and Licensure of Vaccines to Prevent COVID-19

- **Clinical data to support Emergency Use Authorization (EUA) of COVID-19 vaccines**

  - **FDA Guidance (October 2020):**

    Emergency Use Authorization for Vaccines to Prevent COVID-19

- **Continued evaluation of COVID-19 vaccines following licensure or EUA**

Data to Support COVID-19 Vaccine Licensure

FDA

- **Expectation for randomized, blinded, placebo-controlled trials to provide direct evidence that a vaccine protects against SARS-CoV-2 infection and/or disease**

    - Should be feasible given current COVID-19 epidemiology

    - Understanding of how vaccine-elicited immune responses might predict protection is currently too limited to infer COVID-19 vaccine effectiveness from immune responses in the absence of clinical data providing direct evidence of protection

Clinical Trial Populations

FDA

- **Clinical trials to support licensure should enroll adequate numbers of subjects representing populations most affected by COVID-19:**
  - Racial and ethnic minorities
  - Elderly individuals
  - Individuals with medical comorbidities associated with increased risk of severe COVID-19

- **Important to examine safety and effectiveness data in previously infected individuals because pre-vaccination screening for prior infection is unlikely to occur in practice for COVID-19 vaccines**

Effectiveness Endpoints

- **Effectiveness endpoints for Phase 3 trials could be:**

  - **COVID-19 disease of any severity**

  - COVID-19 case definition representing more severe disease

  - SARS-CoV-2 infection, whether or not symptomatic

- **CBER has recommended standardized case definitions to be used in pre-specified analyses**

  - No requirement for any specific endpoint to be used for the primary analysis of vaccine effectiveness

Licensure: Data to Support Effectiveness

FDA

- **Widespread deployment of a weakly effective COVID-19 vaccine could result in more harm than good by:**

  - Providing a false sense of security that interferes with measures to reduce SARS-CoV-2 transmission

  - Interfering with development and evaluation of potentially better vaccines that could have a greater impact on the COVID-19 pandemic

  - Potentially allowing for even less effective vaccines to be deployed based on meeting non-inferiority criteria for relative effectiveness (bio-creep)

- **Without sufficiently stringent effectiveness criteria, the risk of deploying a weakly effective COVID-19 vaccine increases as the number of vaccines being evaluated in Phase 3 trials increases**

Licensure: Data to Support Effectiveness

- **Success criteria for primary vaccine efficacy (VE) endpoint analysis to support licensure of COVID-19 vaccines:**

  – VE point estimate vs. placebo comparator should be ≥50%

  – Appropriately alpha-adjusted confidence interval lower bound should be >30%

- **Secondary VE endpoint analyses to further inform protective effect and to be included in vaccine labeling:**

  – Can be tested against a VE lower bound >0%, provided that primary endpoint criteria are met first

Immunobridging to Infer Effectiveness

- **Direct demonstration of effectiveness may not be feasible in all populations (e.g., pediatrics)**

- **Following direct demonstration of protection in one population, effectiveness of the <u>same vaccine</u> could be inferred in other populations by immunobridging**

  - Based on comparison of immune response biomarker(s) between populations using pre-specified criteria

  - Presumes disease pathogenesis and mechanism of protection in each population are similar

Licensure: Data to Support Safety

- **General expectations are no different than those for safety data that have supported licensure of other preventive vaccines**

  - Safety database of at least 3,000 subjects in relevant age groups (e.g., younger adults and elderly) exposed to the vaccine regimen intended for licensure

- **Safety database for COVID-19 vaccines currently in Phase 3 trials will be substantially larger, with placebo control group**

Licensure: Additional Considerations

- **Data to address important benefit/risk considerations for a COVID-19 vaccine may be limited at the time of a successful case-driven interim or final efficacy analysis**

  - Durability of protective immunity elicited by the vaccine

  - Effectiveness of the vaccine against the most severe and clinically significant manifestations of COVID-19

  - Potential risk of enhanced respiratory disease (ERD) associated with waning of vaccine-elicited immunity

  - Longer-term safety follow-up

- **Additional follow-up after a successful efficacy analysis would inform benefit/risk assessment for licensure as well as labeling**

Overview

- Clinical data to support licensure of COVID-19 vaccines

  - FDA Guidance (June 2020):

    Development and Licensure of Vaccines to Prevent COVID-19

- **Clinical data to support Emergency Use Authorization (EUA) of COVID-19 vaccines**

  - **FDA Guidance (October 2020):**

    Emergency Use Authorization for Vaccines to Prevent COVID-19

- Continued evaluation of COVID-19 vaccines following licensure or EUA

EUA of COVID-19 Vaccines

- **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**

  - In this scenario, a determination that a COVID-19 vaccine's benefits outweigh its risks would require data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and effectiveness sufficient to support widespread use

- **As with vaccine licensure, an EUA would specify use in those populations for which available data support favorable benefit/risk**

Data to Support COVID-19 Vaccine EUA

FDA

- **EUA request for a COVID-19 vaccine may follow a case-driven interim analysis from one or more clinical trials**

- **To support a favorable benefit/risk determination, taking into account rapid and widespread deployment to millions of individuals, including healthy people, vaccine effectiveness should be supported by:**

  - Clinical endpoint that assesses for direct evidence of protection against SARS-CoV-2 infection or disease

  - VE point estimate of ≥50% vs. placebo, with an appropriately alpha-adjusted confidence interval lower bound >30%

Data to Support COVID-19 Vaccine EUA

- **Analyses intended to support issuance of an EUA should:**
  - Ensure that vaccine effectiveness is assessed during the time period when adaptive/memory immune responses (as opposed to innate responses) are mediating protection
  - Allow for early assessment of waning protection and potentially associated risk of ERD
  - Ensure adequate safety follow-up to inform benefit/risk determination

- **CBER considers a median of 2 months to be the minimum follow-up duration that could support a favorable benefit/risk determination to issue an EUA for a COVID-19 vaccine**
  - At least 50% of participants with 2 months of follow-up for safety and effectiveness following completion of the full vaccination regimen

Data to Support COVID-19 Vaccine EUA

FDA

- **Safety considerations supporting a median follow-up of 2 months after completion of the full vaccination regimen:**

  - Historically, uncommon but clinically significant adverse events plausibly linked to vaccines (i.e., immune-mediated adverse reactions) generally have onset within 6 weeks following vaccination*

    *Vaccine Injury Table, National Vaccine Injury Compensation Program (2017)

  - Median follow-up duration of 2 months allows time for potential immune-mediated adverse reactions to be observed and evaluated

- **Timing of planned interim analyses for vaccine efficacy should account for expectations for follow-up to support an EUA**

Data to Support COVID-19 Vaccine EUA

FDA

- **Additional CBER expectations for safety data:**
  - Phase 3 safety data that include a high proportion of enrolled subjects (numbering well over 3,000 vaccine recipients) followed for serious adverse events (SAEs) and adverse events of special interest (AESIs) for at least 1 month after completion of the full vaccination regimen

  - Solicited adverse reactions in an adequate number of subjects to characterize reactogenicity in protocol-defined age cohorts

  - Sufficient cases of severe COVID-19 in placebo recipients, collected in the same timeframe as primary endpoint cases, to assess case split between vaccine vs. placebo groups as signals for effectiveness and for ERD

  - All safety data accumulated from Phase 1 and 2 studies conducted with the vaccine, with focus on SAEs, AESIs, and cases of severe COVID-19

Overview

- **Clinical data to support licensure of COVID-19 vaccines**

  - FDA Guidance (June 2020):

    Development and Licensure of Vaccines to Prevent COVID-19

- **Clinical data to support Emergency Use Authorization (EUA) of COVID-19 vaccines**

  - FDA Guidance (October 2020):

    Emergency Use Authorization for Vaccines to Prevent COVID-19

- **Continued evaluation of COVID-19 vaccines following licensure or EUA**

Continued Evaluation after Licensure or EUA

FDA

- **Safety monitoring during rapid and widespread deployment of a COVID-19 vaccine will be needed to detect and evaluate adverse reactions that may be:**

  – Too uncommon to detect even in large clinical trials

  – Apparent only after additional time to come to medical attention

  – Relevant to specific populations with limited safety data at the time of vaccine deployment (e.g., pregnant women, persons with prior SARS-CoV-2 infection)

Continued Evaluation after Licensure or EUA

FDA

- **Longer-term data on COVID-19 outcomes following licensure or EUA would:**
  - Further characterize duration of protection
  - Determine vaccine effectiveness in populations not included in the initially authorized or approved use
  - Further evaluate effectiveness against specific aspects of SARS-CoV-2 infection or disease
  - Investigate immune biomarkers that might predict protection
  - Further assess theoretical risks of ERD and other potentially immune-mediated complications following vaccination and subsequent exposure to SARS-CoV-2

Continued Evaluation after Licensure or EUA

FDA

- **Evaluation of a COVID-19 vaccine after licensure or EUA should occur through a combination of:**

  - Pharmacovigilance activities, including active and passive safety monitoring, during use of deployed vaccine

  - Continuation of blinded follow-up in ongoing placebo-controlled trials for as long as is feasible

  - Observational studies, including those that leverage healthcare claims data, to evaluate safety and effectiveness outcomes

- **CBER may require post-licensure studies to address known or potential serious risks identified during review of a licensure application**

Passive and Active Safety Monitoring

- **Passive safety monitoring following COVID-19 vaccine licensure or EUA will rely on established reporting mechanisms**
  - Vaccine Adverse Event Reporting System (VAERS)
  - Direct reports to vaccine manufacturer

- **Any EUA request for a COVID-19 vaccine should include a plan for active safety follow-up of persons vaccinated under the EUA**
  - Including but not necessarily limited to deaths, hospitalizations, and other serious or clinically significant AEs
  - To inform ongoing benefit/risk assessments for continuation of the EUA

Continuation of Placebo-Controlled Trials

FDA

- **CBER does not consider issuance of an EUA for a COVID-19 vaccine, in and of itself, as grounds to unblind ongoing clinical trials and offer vaccine to placebo recipients**
  - A COVID-19 vaccine made available under EUA will remain investigational
  - Safety and effectiveness data to support an EUA may be collected under a relatively short follow-up period (median of 2 months following completion of the vaccination regimen) as compared with data that have supported licensure of other preventive vaccines
  - Continuation of placebo-controlled follow-up after EUA will be critical to ensure that additional safety and effectiveness data are accrued to support submission of a licensure application as soon as possible following an EUA
- **Any EUA request for a COVID-19 vaccine should include strategies to ensure follow-up in ongoing trials and to handle loss of follow-up due to withdrawal of participants**

Continuation of Placebo-Controlled Trials

FDA

- **Availability of a licensed vaccine does not automatically preclude continuation of blinded, placebo-controlled trials**
  - In populations for which the licensed vaccine is not approved for use
  - In populations for which the licensed vaccine is not sufficiently available to address public health needs

- **If widespread availability of a licensed COVID-19 vaccine precludes use of placebo comparator:**
  - The licensed COVID-19 vaccine could be used as a comparator to evaluate relative efficacy (rVE) of other vaccines, testing the confidence interval lower bound against a non-inferiority margin
  - Potential to infer effectiveness from comparison of immune responses between vaccines would require further discussion as understanding of mechanism(s) of protection evolves

Extra slides

Case Detection and Confirmation

- **Acute symptomatic cases should be confirmed by virologic methods (e.g., RT-PCR)**

- **Surveillance for infection, including asymptomatic cases, should be included and can be accomplished by:**

  - Virologic methods (with sufficiently frequent sampling)

  - Serologic methods (e.g., detection of antibodies to antigens not included in the vaccine)

- **Clinical assays should be validated as fit for purpose**

CBER Recommended Case Definitions

- **COVID-19 of any severity: virologically confirmed SARS-CoV-2 infection with one or more of the following symptoms:**

  - Fever or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches

  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

CBER Recommended Case Definitions

- **Severe COVID-19: virologically confirmed SARS-CoV-2 infection with one or more of the following signs/symptoms:**

  - Clinical signs at rest (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg)
  - Respiratory failure (need for high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)

  - Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
  - Significant acute renal, hepatic, or neurologic dysfunction
  - Admission to an ICU
  - Death

Licensure: Data to Support Safety

- **Safety database to support licensure should include:**
    - Solicited adverse reactions (e.g., injection site reactions, fever, fatigue) in an adequate number of participants to fully characterize common adverse reactions (reactogenicity)
    - Collection of serious adverse events (SAEs) and adverse events of special interest (AESIs) in all study participants for at least 6 months (or longer, for vaccines with novel adjuvants) following completion of the vaccination regimen
    - Pregnancy outcomes for women vaccinated while pregnant, or within 30 days prior to conception

Licensure: Data to Support Safety

- **Special consideration for safety evaluation of COVID-19 vaccines: enhanced respiratory disease (ERD)**
  - Based on clinical experience with formalin inactivated RSV vaccines in 1960's and observation of post-challenge pulmonary immunopathology in animal studies of some candidate vaccines for other coronaviruses (SARS-CoV, MERS)
  - Associated with vaccine immune response profile characterized by Th2-polarization, low neutralizing vs. binding antibodies
  - Progression of vaccine development to clinical trials with large numbers of participants and/or participants at increased risk of severe COVID-19 requires clinical data (e.g., immune responses) and animal data (e.g., immune responses, challenge studies) to support low risk of ERD
  - Safety data to support COVID-19 vaccine licensure should include favorable case split for severe COVID-19 outcomes (as a marker for ERD) between vaccine vs. placebo groups

Pharmacovigilance

- **Pharmacovigilance plans for COVID-19 vaccines should:**

  - Address routine requirements for preventive vaccines, including periodic safety reports and expedited reporting of serious and unexpected AEs

  - Consider the need for more frequent reporting than routinely required

  - Include specific monitoring for AEs of interest, based on pre-licensure safety database, clinically significant AEs known to be associated with vaccines, and concerns specific to COVID-19 vaccines (i.e., ERD)

  - Consider implementation of a registry to collect information on vaccination during pregnancy and associated pregnancy and infant outcomes

  - Consider the need for structured studies to further evaluate specific risks

EUA Criteria for COVID-19 Vaccines*

FDA

✓ **EUA declaration by HHS Secretary that SARS-CoV-2 can cause a serious or life-threatening disease or condition (March 27, 2020)**

? **Totality of scientific evidence supports that the vaccine may be effective to prevent the serious or life-threatening disease or condition caused by SARS-CoV-2**

? **Known and potential benefits of the vaccine, for its proposed use under EUA, outweigh the known and potential risks**

✓ **No adequate, approved, and available alternative vaccine for preventing the disease or condition caused by SARS-CoV-2**

*Paraphrased from EUA criteria as described in section 564 of FD&C Act (21 U.S.C. 360bbb-3), for the specific case of COVID-19 preventive vaccines