

Considerations on Data to Support Licensure and Emergency Use Authorization (EUA) of COVID-19 Vaccines for Use in Pediatric Populations

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Overview

- General considerations
 - Evaluation of vaccine effectiveness in pediatric populations
 - Evaluation of vaccine safety in pediatric populations
- Data to support licensure and EUA for use in adolescents (12 to <18 years of age)
- Data to support licensure and EUA for use in younger pediatric age groups (6 months to <12 years of age)



General Considerations

- As required by PREA*, a manufacturer applying for FDA licensure of a COVID-19 preventive vaccine would need to provide with the application:
 - Assessments of vaccine safety and effectiveness, OR
 - Request for deferral of studies to assess vaccine safety and effectiveness, OR
 - Request for waiver (with appropriate justification) from requirement to provide assessments of vaccine safety and effectivenessfor all pediatric age groups from birth to <17 years
- Specific scientific/clinical considerations exist for infants <6 months of age; VRBPAC discussion will be limited to age groups 6 months to <18 years

*Pediatric Research Equity Act (2003)

General Considerations

- Extending EUA of a COVID-19 vaccine for use in pediatric age groups (prior to licensure for use in those age groups) could be considered:
 - As needed to address the ongoing COVID-19 public health emergency
 - Provided that statutory criteria for EUA are met, including sufficient data to support that the vaccine's known and potential benefits outweigh known and potential risks in the age group(s) being considered for EUA
- EUA for use in millions of healthy pediatric vaccine recipients would rely on data from at least one well-designed clinical trial that demonstrates the vaccine's safety and effectiveness in a clear and compelling manner
 - Consistent with FDA Guidance, [Emergency Use Authorization for Vaccines to Prevent COVID-19](#)

General Considerations

- VRBPAC is asked to discuss general considerations for safety data to support licensure or EUA of COVID-19 vaccines for use in pediatric age groups from 6 months to <18 years
- VRBPAC is not asked to discuss:
 - Product-specific considerations, including data to support initiation of pediatric trials for specific COVID-19 vaccines and approach to enrollment of specific age groups
 - Data to inform concomitant use of COVID-19 vaccines with other vaccines recommended for routine use in pediatric populations

Evaluating Vaccine Effectiveness



- Clinical endpoint efficacy trial
 - To directly demonstrate prevention of SARS-CoV-2 infection and/or disease
- Immunobridging trial
 - To infer effectiveness based on immune response biomarker(s) elicited by the vaccine in pediatric age group vs. comparator group in which efficacy of the same vaccine was previously demonstrated
 - Presumes disease pathogenesis and mechanism of protection are similar across age groups

Immunobridging Trial

- Should be adequately powered to demonstrate statistically non-inferior immune response in pediatric age group vs. comparator group in which vaccine efficacy previously demonstrated (e.g., adults ages 18-25 years)
- Immune response biomarker(s) should be clinically relevant but need not be established to predict protection against infection or disease
 - Neutralizing antibody responses can be used for immunobridging trials of COVID-19 vaccines, evaluating geometric mean titers and seroresponse rates
 - If an immune response biomarker were established to predict protection at a given threshold, immunobridging can be based on seroresponse rates alone
- Should plan for efficacy endpoint analyses, as feasible (can be descriptive)

Immunobridging Trial



- Features of scientifically rigorous pediatric immunobridging trials:
 - Pediatric and adult comparator groups are similar with respect to demographic variables (other than age), baseline health status, and prior exposure to SARS-CoV-2 infection or vaccination (i.e., naïve)
 - Comparator group need not be concurrently enrolled in the same trial if adequate measures to mitigate against introduction of bias in participant selection and conduct of immunogenicity assays and analyses
 - Sufficiently stringent statistical success criteria (e.g., non-inferiority margins of 1.5-fold for geometric mean titers and -10% for seroresponse rates)
 - Data to support use of immune biomarker(s) if inferring effectiveness of lower dose level than evaluated in successful adult efficacy trial

Evaluating Vaccine Safety

- General approach to safety evaluation in COVID-19 vaccine pediatric trials is no different than for other preventive vaccines for infectious diseases:
 - Common injection site and systemic adverse reactions solicited for ~1 week after each study vaccination
 - All adverse events (AEs) collected for ~1 month after each vaccination
 - Serious and other medically attended AEs and AEs of special interest (including severe COVID-19 and MIS-C) collected for the duration of study - at least 6 months, and ideally 1 year or longer, after last vaccination
 - Comparator group (ideally placebo control), followed for as long as feasible
- Some adverse reactions (e.g., myopericarditis) may be too infrequent to detect in a safety database of typical size for pre-licensure clinical trials

Evaluating Vaccine Safety

- COVID-19 vaccines represent a novel class of preventive vaccines, with some candidates also representing novel vaccine platforms
 - Overall safety database for pediatric age groups should generally approach ~3,000 trial participants vaccinated with the age-appropriate dosing regimen intended for licensure or authorization and followed for at least 6 months after completion of the vaccination regimen
 - Safety database should include adequate representation across age groups, especially younger age groups that are less physiologically similar to adults
- Available safety data from clinical trials and post-licensure/post-authorization use in older age groups (e.g., younger adults) would be considered in risk assessment for each pediatric age group

Licensure in Adolescents

- Evidence of effectiveness from an immunobridging trial (plus descriptive clinical endpoint efficacy data, as available)
- Safety database of at least 1,000 younger adolescents (12 to <16 years of age) and up to several hundred older adolescents (16 to <18 years of age) with median 6 months follow-up after completion of vaccination regimen
 - Plus, adequately sized control group (ideally placebo)
 - Supplemented with available safety data from clinical trials and post-authorization/post-licensure use in adults
- Older adolescents could be included in original licensure application for use in adults, if included in adult efficacy trial

EUA in Adolescents

- Evidence of effectiveness from an immunobridging trial (plus descriptive clinical endpoint efficacy data, as available)
- Same size clinical trial safety database as for licensure, with median 2 months follow-up after completion of vaccination regimen
 - Supplemented with available safety data from clinical trials and post-authorization/post-licensure use in adults
 - Similar approach to safety data for EUA in adults
 - Reflected by May 2021 extension of EUA for Pfizer-BioNTech COVID vaccine for use in adolescents 12 to <16 years of age
- Older adolescents (16 to <18 years of age) could be included in EUA for use in adults, if included in adult efficacy trial

Licensure in Younger Age Groups



- Evidence of effectiveness from an immunobridging trial (plus descriptive clinical endpoint efficacy data, as available)
 - For immunobridging trial, independently powered for each of several age groups (e.g., 6 to <12 years, 2 to <6 years, and 6 months to <2 years) vaccinated with the age-appropriate dosing regimen intended for licensure
- Safety database of at least 1,000 vaccine recipients in each age group vaccinated with the age-appropriate dosing regimen intended for licensure and with median 6 months follow-up after completion of vaccination series
 - Plus, adequately sized age-specific control groups (ideally placebo)
 - Supplemented with available safety data from clinical trials and post-authorization/post-licensure use in older age groups



EUA in Younger Age Groups

- Considerations for whether to extend a COVID-19 vaccine EUA for use in younger pediatric age groups (<12 years) would include:
 - Trajectory of COVID-19 epidemiology in the US
 - Burden of COVID-19 in younger age groups, and therefore anticipated benefits
 - Robustness of available safety data (including from experience in older age groups) to inform risk assessment
- A conclusion of clear and compelling safety and effectiveness to support EUA (and need for EUA) may be less certain for younger pediatric age groups than for adolescents and adults



EUA in Younger Age Groups

- Data that could potentially support EUA for each of several age groups (e.g., 6 to <12 years, 2 to <6 years, and 6 months to <2 years):
 - Evidence of effectiveness from an immunobridging trial (plus descriptive clinical endpoint efficacy data, as available)
 - Same size clinical trial safety database as for licensure, with sufficient duration of follow-up to assess risk, considering:
 - Anticipated benefits in younger pediatric age groups
 - Available safety data from clinical trials and post-licensure/post-authorization experience in older age groups (i.e., adolescents and adults)
 - Physiologic differences between younger pediatric age groups vs. older age groups

Items for VRBPAC Discussion (no vote)

1. Provided there is sufficient evidence of effectiveness to support benefit of a COVID-19 preventive vaccine for pediatric age groups (e.g., 6 to <12 years, 2 to <6 years, and 6 months to <2 years), please discuss the safety data, including database size and duration of follow-up, that would support:
 - a. Emergency Use Authorization
 - b. Licensure



Items for VRBPAC Discussion (no vote)

2. Provided there is sufficient evidence of effectiveness to support benefit of a COVID-19 preventive vaccine for adolescents 12 to <18 years of age, please discuss the safety data, including database size and duration of follow-up, that would support licensure.

Items for VRBPAC Discussion (no vote)

3. Please discuss studies following licensure and/or issuance of an EUA to further evaluate safety and effectiveness of COVID-19 vaccines in different pediatric age groups.



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