Vaccines and Related Biological Products Advisory Committee Meeting
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FDA Briefing Document

Licensure and Emergency Use Authorization of Vaccines to Prevent COVID-19 for Use in Pediatric Populations

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Glossary

BEST	Biologics Effectiveness and Safety
BLA	biologics license application
CBRN	chemical, biological, radiological, or nuclear
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMS	Centers for Medicare and Medicaid Services
COVID-19	coronavirus disease 2019
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GMT	geometric mean titer
HHS	US Department of Health and Human Services
IND	investigational new drug
PMC	post-licensure commitment
PMR	post-licensure requirement
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VRBPAC	Vaccines and Related Biological Products Advisory Committee
MIS-C	multisystem inflammatory syndrome in children
PREA	Pediatric Research Equity Act
PVP	Pharmacovigilance Plan
VE	vaccine efficacy
CDC	Centers for Disease Control and Prevention
VAERS	Vaccine Adverse Event Reporting System
VOC	variant of concern
VSD	Vaccine Safety Datalink
US	United States

1. BACKGROUND

1.1. SARS-CoV-2 Pandemic

1.1.1. Impact of the ongoing SARS-Co-V-2 pandemic

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to present an extraordinary challenge to global health and, as of May 25, 2021, has caused approximately 167 million cases of COVID-19 and 3.4 million deaths worldwide.[1] In the United States (US), more than 32 million cases have been reported to the Centers for Disease Control and Prevention (CDC). The emergence of SARS-CoV-2 variants with multiple mutations in the SARS-CoV-2 spike (S) protein in the United Kingdom (B.1.1.7 lineage), Brazil (P.1 lineage), and South Africa (B.1.351 lineage), has raised concerns regarding increased transmission rates; these variants of concern (VOCs) account for 66.2%, 5.2%, and 0.8% of SARS-CoV-2 lineages circulating in the US as of April 21, 2021.[2]

A comprehensive national public health effort to control SARS-CoV-2 and reduce community transmission includes: COVID-19 vaccination programs; guidance on protective measures (e.g., masking, physical distancing); contact tracing; expanded distribution and access to SARS-CoV-2 testing; and increased surveillance capabilities to monitor existing and emerging VOCs, and ongoing, real-time safety monitoring. All of these measures will be critical to saving lives, safely reopening schools, and restoring economic activities.

1.1.2. COVID-19 in pediatric populations versus adults

As of May 25, 2021, approximately 553,000 and 2.7 million COVID-19 cases, respectively, were reported in children 0-4 and 5-17 years of age in the US, among which 121 (0.02%) and 278 (0.01%), respectively, were fatal, and more than 38,000 of which resulted in hospitalizations reported since August 1, 2020, in patients 0-17 years of age.[3] Children and adolescents appear less susceptible to SARS-CoV-2 infection and have a milder COVID-19 disease course as compared with adults.[4,5] In a meta-analysis of 32 contact tracing or population testing studies comparing SARS-CoV-2 prevalence in children and adults, children younger than 14 years were about half as likely to be infected from an index case (OR: 0.56, 95% CI 0.37-0.85), while the likelihood of infection among children ≥14 years was similar to adults.[5]

As with adults, children and adolescents with underlying conditions such as asthma, chronic lung disease, and cancer are at higher risk than their heathier counterparts for COVID-19-related hospitalization and death.[6] Of the children who developed severe illness from COVID-19, most have had underlying medical conditions.[7] Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious COVID-19-associated condition that can present with persistent fever, laboratory markers of inflammation and heart damage, and, in severe cases, hypotension and shock.[7] For some children, ongoing COVID-19 symptoms continue for weeks to months after their initial illness.[8] Between May 2020 and March 2021, the CDC received reports of 3,185 cases and 36 deaths that met the definition for MIS-C; most cases occurred in children ages 1 to 14 years (median age 9 years), in males (59%), and in children who were reported as Hispanic or Black (64%).[9]

COVID-19 pandemic has disproportionately affected young people of racial and ethnic minority groups. In an analysis of 689,672 US COVID-19 cases among persons <25 years of age reported to the CDC during 2020, COVID-19 incidence ranged from 35 cases per 100,000 among White persons to 163 per 100,000 among American Indian or Alaska Native persons. Compared with White persons, rates were higher among American Indian or Alaska Native (RR

= 4.62), Hispanic (RR = 3.87), Native Hawaiian and Pacific Islander (RR = 2.49), Black (RR = 2.46), and Asian persons (RR = 1.53) and were approximately equal among multiracial persons (RR = 1.09).[10]

1.2. US requirements to support licensure of a BLA for a biological product

A single set of basic regulatory requirements applies to all vaccines, regardless of the technology used to produce them. Section 351 of the Public Health Service Act (42 USC 262) states that a biologics license application (BLA) can be approved based on a demonstration that "…(a) the biological product that is the subject of the application is safe, pure and potent; and (b) the facility in which the biological product is manufactured, processed, packed or held meets standards designed to assure that the biological product continues to be safe, pure, and potent...". Thus, regardless of indication or intended target population, only those COVID-19 vaccines that are demonstrated to be safe and effective and that can be manufactured in a consistent manner will be licensed by the FDA.

1.2.1. Information needed to support licensure of COVID-19 vaccines

To facilitate the manufacturing, clinical development, and licensure of COVID-19 vaccines, FDA published the guidance for industry entitled Development and Licensure of Vaccines to Prevent COVID-19 (June 2020) describing FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19.[11] This guidance provides an overview of key considerations to satisfy regulatory requirements set forth in the investigational new drug application (IND) regulations in 21 CFR Part 312 and licensing regulations in 21 CFR Part 601 for chemistry, manufacturing, and controls (CMC), and nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation of COVID-19 preventive vaccines. The guidance notes that the efficacy of COVID-19 vaccines should be demonstrated in adequate and well controlled clinical trials that directly evaluate the ability of the vaccine to protect humans from SARS-CoV-2 infection and/or disease. The guidance notes further that safety evaluations including the size of the database required to support licensure should be no different than for other preventive vaccines for infectious diseases.

1.3. US requirements to support issuance of an EUA for a biological product

Based on the declaration by the Secretary of the US Department of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[12]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.

- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can authorize unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one Phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and would continue under further investigation (under an Investigational New Drug Application). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

1.3.1. Information needed to support EUA of COVID-19 vaccines

An EUA of a COVID-19 vaccine allows for the rapid and widespread deployment for administration to millions of individuals, including healthy people and thus, data are needed demonstrating that the known and potential benefits of the vaccine outweigh its known and potential risks. FDA published guidance for industry Emergency Use Authorization for Vaccines to Prevent COVID-19 (February 2021, originally issued October 2020) describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[13] Issuance of an EUA for a COVID-19 vaccine would require adequate manufacturing information to ensure its quality and consistency and a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.

1.4. Licensure and EUA of COVID-19 vaccines for use in pediatric populations

These requirements summarized under Sections 1.2 and 1.3 would also apply to licensure and emergency use authorization of COVID-19 vaccines for use in the pediatric population. Of note, as described in the guidance for industry entitled Development and Licensure of Vaccines to Prevent COVID-19 (June 2020), the timing, design and endpoints for pediatric studies would be discussed in the context of specific vaccine development programs.

FDA acknowledges that direct demonstration of effectiveness in field efficacy trials may not be feasible in pediatric populations and thus, following direct demonstration of protection in adults, effectiveness of the same vaccine could be inferred in pediatric populations by immunobridging.

This approach will need to be based on comparison of immune response biomarker(s) between the pediatric and adult populations using pre-specified criteria and presumes that disease pathogenesis and mechanism of protection in each population are similar. Additional considerations are summarized in Section 2.1 of this document.

1.5. Available vaccines and therapies for COVID-19 for the pediatric population

No vaccine or other medical product is FDA approved for prevention of COVID-19. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. FDA subsequently issued EUAs for two monoclonal antibody combinations (casirivimab/imdevimab and bamlanivimab/etesevimab) for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to severe COVID-19 and/or hospitalization. FDA has issued EUAs for three COVID-19 vaccines as shown in Table 1 below.

Table 1. Emergency Use Authorizations of COVID-19 Vaccines

Sponsor	Regimen	Indicated Population	Date of EUA
Pfizer	2 doses 3 weeks apart	Individuals ≥16 years of age	December 11, 2020
Moderna	2 doses 4 weeks apart	Adults ≥18 years of age	December 18, 2020
Janssen	Single dose	Adults ≥18 years of age	February 27, 2021
Pfizer (amendment)	2 doses 3 weeks apart	Individuals ≥12 years of age	May 10, 2021

These COVID-19 vaccines are considered unapproved products for purposes of the emergency use standard. In addition, there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition for the pediatric population less than 12 years of age.

1.6. Previous meetings of the VRBPAC to discuss vaccines to prevent COVID-19

On October 22, 2020, the VRBPAC met in open session to discuss, in general, the development, authorization, and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents
- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine
- 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.

On December 10, 2020, the VRBPAC met in open session to discuss the EUA request of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age older. Topics discussed at the meeting but not voted upon included Pfizer's plan for continuation of blinded, placebo-controlled follow-up in ongoing trials in the event that the vaccine is made available under EUA and gaps in plans for further evaluation of vaccine safety and effectiveness in populations that receive the Pfizer-BioNTech Vaccine under an EUA. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the proposed vaccine outweigh its risks for use in individuals 16 years of age and older.

On December 17, 2020, the VRBPAC met to discuss the EUA request of the Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Committee members discussed but did not vote on whether the ongoing Phase 3 trial should be continued using a blinded cross-over design or an open-label design as proposed by Moderna. As part of that discussion, committee members suggested the conduct of additional studies to obtain data, including data on vaccine effectiveness in the elderly, immunogenicity in immunocompromised subpopulations, effectiveness of the vaccine following one dose, and the vaccine's duration of protection. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the proposed vaccine outweigh its risks for use in individuals 18 years of age and older.

On February 26, 2021 the VRBPAC met to discuss the EUA request of the Janssen COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Committee members discussed but did not vote on how data from the currently ongoing phase 3 clinical trial evaluating a two dose schedule will impact the use of the product when authorized under the EUA as a single dose; in particular, if a two dose regimen demonstrates improved efficacy and immunogenicity. As part of that discussion, committee members suggested that additional data should be obtained on efficacy of the vaccine in subjects SARS-CoV-2 positive at baseline and data on rates of asymptomatic infections in vaccinated subjects. The importance of assessing neutralizing ability of sera derived from subjects vaccinated with the current vaccine construct against emerging SARS-CoV-2 variants of concern was highlighted. Overall, committee members did not express concern about vaccine efficacy (VE) among older adults with or without comorbidities. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the proposed vaccine outweigh its risks for use in individuals 18 years of age and older.

2. DATA TO SUPPORT LICENSURE OR EUA OF COVID-19 PREVENTIVE VACCINES FOR USE IN PEDIATRIC POPULATIONS

This section discusses general considerations for data to support licensure or emergency use authorization of COVID-19 preventive vaccines for use in pediatric populations. These considerations would apply to COVID-19 vaccines that have already been licensed or received emergency use authorization for use in adults. While the VRBPAC will not be asked to discuss specific COVID-19 vaccines, product-specific considerations may warrant additional data to support licensure or emergency use authorization (e.g., a larger safety database or longer duration of follow-up in pediatric clinical trials to investigate a risk associated with a vaccine component or identified in clinical trials or post-licensure/post-authorization use).

Preventive vaccines for COVID-19 will generally be subject to requirements of the Pediatric Research Equity Act (PREA),[14] meaning that absent a scientifically and statutorily acceptable justification for a waiver, a manufacturer of a FDA-licensed COVID-19 vaccine would be required to submit to FDA assessments of the safety and effectiveness of the vaccine in all pediatric age groups. Due to the age de-escalation approach typically undertaken for vaccine development in pediatric populations, typically starting with adolescents and proceeding downward in age as safety and effectiveness data are accrued, licensure or emergency use authorization of COVID-19 vaccines for use in pediatric age groups may proceed in a similarly step-wise fashion. While COVID-19 may affect all pediatric age groups, several complexities impact vaccine development specifically for use in younger infants <6 months of age, including the potential for maternally transferred antibodies to confer protection, increased potential for severe reactogenicity with decreasing age, and the need to account for concomitant use of a COVID-19 vaccine with multiple, closely-spaced routine immunizations. Younger infants would

likely be the last age group enrolled in pediatric trials of COVID-19 vaccines, dependent on prior rigorous evaluation of safety and effectiveness (and dose ranging) in older pediatric age groups, and emerging data may provide a basis to justify a waiver from PREA requirements for assessment of COVID-19 vaccines in younger infants. Considering the above factors, the VRBPAC will be asked to focus their discussion on data to support licensure or emergency use authorization of COVID-19 vaccines for use in pediatric populations 6 months to <18 years of age.

FDA recognizes that for practical reasons, concomitant use of COVID-19 preventive vaccines with other routinely recommended immunizations may be desirable in all pediatric age groups. Consequently, FDA encourages COVID-19 vaccine manufacturers to include in their pediatric development, studies to inform the safety and effectiveness (i.e., absence of immune interference) of COVID-19 vaccines when used concomitantly with other preventive vaccines. However, consistent with longstanding regulatory approach to preventive vaccines for infectious diseases, FDA will not require vaccine manufacturers to assess concomitant administration to support licensure or emergency use authorization of COVID-19 vaccines for use in pediatric populations.

As with adults, available data indicate that children in communities of color have been disproportionately impacted by COVID-19, whether due to biological factors or to effects of healthcare disparities.[11] Therefore, FDA strongly encourages COVID-19 vaccine manufacturers to enroll populations most affected by COVID-19, specifically racial and ethnic minorities, in pediatric trials of COVID-19 vaccines.

Determination of when to initiate pediatric trials (including in specific age groups) is beyond the scope of the discussion for this VRBPAC meeting. Acknowledging that COVID-19 affects all age groups, FDA generally expects that pediatric trials would be initiated in specific age groups as soon as available data support that the vaccine would confer a prospect of direct benefit and acceptable risk to trial participants (21 CFR 50.52). This determination will be made in the context of specific vaccine development programs and following discussion of study design elements that ensure participant safety and compliance with 21 CFR Part 50 Subpart D regulations providing additional safeguards for children in clinical investigations.[15] However, VRBPAC discussion of the approaches to evaluating safety and effectiveness described in the following sections will help FDA to advise COVID-19 vaccine manufacturers to ensure that pediatric trials will be adequately designed to support vaccine licensure (or emergency use authorization, when relevant statutory criteria are met) in various age groups.

2.1. Evaluation of COVID-19 vaccine effectiveness in pediatric populations

Effectiveness of COVID-19 vaccines in pediatric populations could be demonstrated directly in efficacy field trials that evaluate clinical disease endpoints related to SARS-CoV-2 infection and/or disease. Anticipating that adequately powered field efficacy trials in pediatric populations may not be feasible (especially for the most severe and clinically significant outcomes such as MIS-C), effectiveness in pediatric populations may be inferred through an immunobridging approach in which an immune response biomarker(s) elicited by the vaccine in pediatric populations is compared to the same biomarker(s) elicited by the vaccine in another population (i.e., adults) for which effectiveness of the vaccine has already been demonstrated. Considerations for clinical endpoint efficacy and immunobridging approaches are described in greater detail below.

2.1.1. Clinical endpoint efficacy trials

A field efficacy trial that is intended to provide the primary source of evidence to demonstrate effectiveness of a COVID-19 vaccine in a pediatric population would be adequately powered for formal hypothesis testing on at least the primary efficacy endpoint(s), if not also secondary efficacy endpoints. Field efficacy trials could evaluate a COVID-19 vaccine candidate against a placebo control or against an active comparator already demonstrated to be effective in the age group(s) enrolled in the trial. As described in the FDA guidance Development and Licensure of Vaccines to Prevent COVID-19 (June 2020), sufficiently stringent pre-specified success criteria for the primary efficacy endpoint analysis would mitigate against deployment of a weakly effective vaccine and therefore ensure that the vaccine would be likely to make a meaningful impact on prevention of COVID-19 and the COVID-19 pandemic. The success criteria outlined in the June 2020 FDA guidance were informed mainly by the burden of COVID-19 disease in adult populations. For a placebo-controlled trial, sufficiently stringent success criteria include at least 50% for the VE point estimate and >30% for the lower bound of the associated appropriately alpha-adjusted confidence interval. For an active comparator-controlled trial, a sufficiently stringent success criterion is a lower bound of >-10% for the appropriately alpha-adjusted confidence interval around the relative VE point estimate.

The incidence and severity of COVID-19 disease in pediatric populations, especially in younger age groups, are generally lower than in adults. Depending on epidemiologic trends, an adequately powered clinical endpoint efficacy trial with sufficient case accrual across pediatric age groups may be very difficult, if not infeasible, to conduct. Furthermore, in considering the balance of benefits and risks to support licensure or emergency use authorization of COVID-19 vaccines for use in pediatric populations, it could be argued that the lower burden of disease in pediatric populations might warrant more stringent success criteria than for adults, at least for placebo-controlled trials. A very high VE point estimate, with a narrow confidence interval, observed in studies in adults might also warrant more stringent success criteria in pediatric trials to ensure that the vaccine is as effective in pediatric populations as it is in adult populations. Conversely, an argument could be made that demonstration of very high VE in adults could allow for a less stringent success criterion for the VE confidence interval lower bound in pediatric trials (and thus a smaller number of primary endpoint cases needed), provided that the VE point estimate is similar to that observed in adults. The choice of primary endpoint may also inform appropriately stringent success criteria for placebo-controlled pediatric trials, as data demonstrating prevention of infection (rather than prevention of disease, or prevention of severe disease) may be less likely for children vs. adults.

2.1.2. Immunobridging trials

As noted above, the attack rate for SARS-CoV-2 infection and/or disease in pediatric populations may not be high enough to support the timely completion of adequately powered field efficacy trials. If a COVID-19 vaccine development program has met FDA expectations for data to support effectiveness in adults (and presuming that disease pathogenesis and mechanism of protection are sufficiently similar across adult and pediatric populations), effectiveness in pediatric populations may be inferred by immunobridging. In this approach, an immune response biomarker(s) elicited by the vaccine in a pediatric age group is compared to the same immune response biomarker(s) elicited by the same vaccine in a relevant adult age group, with formal statistical hypothesis testing to demonstrate that the measured immune response in the pediatric age group is non-inferior to that in adults. If an immune response biomarker (at a given threshold) is established to predict protection against infection and/or disease, that biomarker can be used for immunobridging by comparing the proportions of

vaccine recipients in each population who attain the given threshold post-vaccination. However, an immune response biomarker that is not scientifically established to predict protection at a given threshold may be used for immunobridging so long as available data support that the biomarker is clinically relevant to vaccine-elicited protective immunity. Examples of this approach include vaccines approved for use in pediatric populations to prevent HPV (immunobridging using type-specific anti-HPV IgG antibodies) and cholera (immunobridging using serum vibriocidal antibodies).

Based on available data[16] (and similar to the approach outlined in the February 2021 update of the FDA guidance Emergency Use Authorization for Vaccines to Prevent COVID-19 for evaluation of modified COVID-19 vaccines intended to address emerging SARS-CoV-2 variants), neutralizing antibodies can serve as a biomarker to infer COVID-19 vaccine effectiveness in pediatric populations via immunobridging. Because no specific neutralizing antibody titer has yet been established to predict protection, rigorous immunobridging studies would compare the range of neutralizing antibody responses in adult vs. pediatric populations by evaluating both seroresponse rates, using a -10% non-inferiority margin, and geometric mean titers (GMTs), using a 1.5-fold non-inferiority margin, at a given time point (e.g., 1 month after completion of the vaccination regimen, around the time when peak antibody responses are expected). These non-inferiority margins are generally considered to be necessarily stringent for immunobridging, although with adequate justification alternate non-inferiority margins may be acceptable. As pediatric vaccine development may involve dose ranging to avoid undesirable reactogenicity, a deeper understanding of the relationship between neutralizing antibody titers and protection against SARS-CoV-2 infection or disease than currently available may be needed to support immunobridging to infer effectiveness of a pediatric dose level that is lower than the dose level demonstrated to be effective in an adult efficacy trial.

Because the dose-response relationship may vary across pediatric age groups, adequately powered immunobridging analyses would ideally be conducted independently for several age groups (e.g., adolescents 12 to <18 years of age, school-age children 6 to <12 years of age, younger children 2 to <6 years of age, and infants and toddlers 6 months to <2 years of age). To mitigate against bias introduced by biological differences between pediatric and adult populations, the immunobridging comparator group would represent the youngest age group included in a successful clinical endpoint efficacy trial with formal hypothesis testing on sufficiently stringent success criteria (e.g., younger adults 18-25 years of age). The pediatric and adult populations contributing to immunobridging analyses would also ideally be similar with regard to demographic variables other than age and naïve to SARS-CoV-2 infection through the primary immunogenicity endpoint assessment period. The pediatric and adult populations need not be enrolled concurrently in the same trial, provided that adequate measures exist to mitigate against introduction of bias when selecting trial participants for inclusion in analysis populations, conducting immunogenicity assays, and analyzing data.

In situations where vaccine manufacturers intend immunobridging trials to provide the primary source of evidence to support vaccine effectiveness in pediatric populations, FDA encourages those manufacturers to directly evaluate vaccine efficacy against SARS-CoV-2 infection and/or disease as well, to the extent feasible. Planned analyses of VE in these trials could be descriptive, without formal hypothesis testing, though further consideration would be needed if case splits between vaccine and placebo groups were not consistent with vaccine effectiveness.

2.2. Evaluation of COVID-19 vaccine safety in pediatric populations

As outlined in the FDA guidance Development and Licensure of Vaccines to Prevent COVID-19 (June 2020), safety data to support licensure of COVID-19 vaccines would generally be the same as for other preventive vaccines for infectious diseases. These safety data would include characterization of common adverse reactions (reactogenicity, including injection site and systemic adverse reactions), as well as less common but medically important adverse reactions. Depending on the age groups intended for use, prior experience with the vaccine in adults, and prior experience with licensed vaccines based on the same or similar platforms, FDA has accepted an overall pediatric safety database in the range of ~500 to ~3,000 trial participants exposed to the age-appropriate dose and regimen intended for licensure and followed for at least 6 months after completion of the vaccination regimen as adequate to support licensure of preventive vaccines for infectious diseases. Since COVID-19 vaccines represent a new class of vaccines, with many of the lead candidates based on new platform technologies, an appropriate overall pediatric safety database would approach the upper end of this range, with adequate representation across all pediatric age groups, in particular younger age groups (e.g., <12 years) that are less physiologically similar to adults. A control group (ideally placebo control) would be important to inform interpretation of safety data and to comply with the expectation for adequate and well-controlled studies to support licensure. If another COVID-19 vaccine is licensed or authorized for use in the age group(s) enrolled in the trial, recommended by public health authorities, and widely available such that it is unethical to use a placebo control, the licensed or authorized COVID-19 vaccine could serve as a control.

Within the overall pre-licensure safety database, solicited reactogenicity could be adequately characterized among several hundred trial participants in each relevant age group. Additionally, safety evaluation in all trial participants would include collection of all adverse events through at least one month after each study vaccination and collection of serious and other medically attended adverse events for the duration of the trial. Although longer-term follow-up (through 1 year or longer post-vaccination) of trial participants would be important to ongoing assessment of both benefits and risks, completion of such longer-term follow-up would not be a prerequisite to licensure unless warranted by a specific safety concern. Post-licensure/post-authorization safety surveillance and observational studies in pediatric populations would be needed to evaluate for adverse reactions that occur too rarely to be detected in clinical trials.

Emergency use authorization of a COVID-19 vaccine for use in pediatric populations would require a determination that the known and potential benefits of the vaccine outweigh the known and potential risks specifically in the age groups being considered for emergency use authorization. Therefore, clear and compelling evidence to support the safety of the vaccine would be expected to justify its authorization for emergency use in millions of healthy children. For a given pediatric age group, such evidence would be expected to include a similarly sized pediatric safety database as that which would support vaccine licensure, plus available supportive safety data from clinical trial and post-licensure/post-authorization experience in adults and older pediatric age groups. The duration of follow-up that FDA and the VRBPAC have considered to be adequate to support emergency use authorization of COVID-19 vaccines for use in adults (overall safety database with a median of 2 months follow-up after completion of the vaccination regimen) is less than the duration of follow-up expected to support vaccine licensure. This approach was based on the epidemiology of COVID-19 and demonstrated benefits of authorized vaccines in adult age groups and sought to balance the need to address the ongoing pandemic against additional safety data that could be accrued from longer follow-up. A similar approach could be taken for pediatric populations but would need to consider trends in COVID-19 epidemiology, expected benefits of vaccination in respective pediatric age

groups, and relatively smaller safety database size for pediatric immunobridging trials as compared with field efficacy trials conducted in adults. These considerations may be different for younger vs. older pediatric age groups.

Evaluation for the theoretical risk of vaccine-enhanced disease has been a point of focus in FDA guidance on the development, licensure, and emergency use authorization of COVID-19 vaccines.[11,13] While the totality of available data to date have not raised concerns for vaccine-enhanced disease associated with any of the COVID-19 vaccines authorized for use in adults, evaluation of severe COVID-19 outcomes among vaccine recipients (in particular MIS-C, if such cases were to occur) remains an important component of clinical trials, post-licensure/post-authorization surveillance, and observational studies of COVID-19 vaccines in pediatric populations.

2.3. Considerations for licensure and EUA of COVID-19 vaccines for use in adolescents (12 to <18 years of age)

2.3.1. Licensure of BLA supplements for use in adolescents

As discussed in Sections 2.1 and 2.2 above, a placebo-controlled immunobridging and safety trial with or without supportive descriptive clinical endpoint efficacy data (as feasible) could provide evidence of vaccine safety and effectiveness to support licensure of a COVID-19 vaccine for use in adolescents. This approach would follow a successful efficacy trial supporting licensure of the vaccine for use in the immunobridging comparator group (e.g., adults 18-25 years of age). Alternatively, an adequately powered clinical endpoint efficacy trial with formal hypothesis testing could provide evidence of vaccine effectiveness in adolescents, although questions about appropriately stringent success criteria and feasibility of conducting such trials would need to be addressed. Older adolescents (e.g.,16 to <18 years of age, who are physiologically most similar to younger adults) could potentially be included in licensure applications for use in adults if participants in this age group were also included in a successful adult efficacy trial; even if few efficacy endpoint cases were accrued in older adolescents enrolled in an adult efficacy trial, vaccine effectiveness in older adolescents could be inferred by extrapolation.

FDA has advised COVID-19 vaccine manufacturers that a safety database adequate to support licensure should include at least 500 vaccine recipients 12 to <16 years of age (and up to several hundred trial participants 16 to <18 years of age if not included in adult efficacy trials) followed for at least 6 months after completion of the vaccination regimen. An adolescent safety database that includes at least 1,000 vaccine recipients 12 to <16 years of age with a median follow-up of at least 6 months after completion of the vaccination regimen would not only satisfy the above expectation for this age group but would also provide for a more robust overall safety database. This safety database approach presumes that no safety concerns are identified that would warrant evaluation in a larger number of adolescent vaccine recipients. Assessment of risks in adolescents would also include available safety data from pre-licensure trials and post-licensure/post-authorization use in adults.

2.3.2. EUA for use in adolescents

Considering the current epidemiology of COVID-19 in the US, emergency use authorization of COVID-19 vaccines for use in adolescents may be justified by clear and compelling evidence of safety and effectiveness from at least one adequate and well-controlled clinical trial in this age group (e.g., a clinical endpoint efficacy trial or an immunobridging trial). In considering the

clinical features and epidemiology of COVID-19 in adolescents, their physiologic similarity to adults, and general experience with preventive vaccines in this age group, FDA has advised vaccine manufacturers that consistent with the October 2020 guidance, a median follow-up of at least 2 months after completion of the vaccination regimen in adolescent clinical trial participants would provide sufficient safety data to assess risks for emergency use authorization. This median follow-up would apply to the same adolescent safety database as described above to support licensure, which would include at least 1,000 vaccine recipients 12 to <16 years of age. Data sufficient to support emergency use authorization or licensure of the vaccine for use in adults would provide support for emergency use authorization in adolescents, and available longer-term safety data and post-licensure/post-authorization experience in younger adults would be included in the assessment of risks for adolescents. Older adolescents 16 to <18 years of age could be included in an emergency use authorization either with adults or with younger adolescents, based on safety evaluation and available immunogenicity or clinical endpoint efficacy data in up to several hundred vaccine recipients in this age group, and extrapolation as needed.

The above approach to emergency use authorization in adolescents is reflected by recent experience with the Pfizer-BioNTech COVID-19 vaccine. Following emergency use authorization for ages 16 years and older in December 2020 based on the results of a successful clinical endpoint efficacy trial,[17] a placebo-controlled immunobridging and safety evaluation in >2,200 trial participants 12 to <16 years of age (including >1,100 vaccine recipients with a median follow-up of more than 2 months after completion of the vaccination regimen) supported amending the emergency use authorization in May 2021 to include younger adolescents in this age group.[18] FDA anticipates that emergency use authorization requests for other COVID-19 vaccines for use in adolescents would follow this same approach.

2.4. Considerations for licensure and EUA of COVID-19 vaccines for use in younger pediatric age groups (6 months to <12 years of age)

2.4.1. Licensure of BLA supplements for use in younger pediatric age groups

Evidence of vaccine effectiveness to support licensure of a COVID-19 vaccine for use in younger pediatric age groups could be provided as described above for adolescents. Immunobridging, with or without supportive descriptive clinical endpoint efficacy data, would likely be the most feasible approach in these age groups. Given the generally lower incidence and severity of disease in these age groups, any proposal for a clinical endpoint efficacy trial with formal hypothesis testing to demonstrate vaccine effectiveness would address considerations for appropriately stringent success criteria as described in Section 2.1.1.

To adequately assess risks in pre-licensure clinical trials, the safety database for each of several age groups (e.g., adolescents 12 to <18 years of age, school-age children 6 to <12 years of age, younger children 2 to <6 years of age, and infants and toddlers 6 months to <2 years of age) could include at least 1,000 vaccine recipients, plus control recipients, followed for a median of at least 6 months after completion of the vaccination regimen. As with adolescents, this safety database approach presumes that no safety concerns are identified that would warrant evaluation in a larger number of younger pediatric vaccine recipients. Safety data from clinical trials and post-licensure/post-authorization experience in adults and older pediatric age groups would also inform the risk assessment for each younger pediatric age group.

2.4.2. EUA for use in younger pediatric age groups

In considering the prospect of emergency use authorization of a COVID-19 vaccine for use in younger pediatric age groups, a central question is the circumstances under which the known and potential benefits of making an effective COVID-19 vaccine available to these age groups would outweigh the known and potential risks. Assuming that pre-licensure trials in younger pediatric age groups will primarily focus on immunobridging to infer vaccine effectiveness and will include the numbers of participants discussed in Section 2.4.1 above, the following considerations may be relevant: 1) epidemiological trends for COVID-19 in these younger age groups as well as in adolescents and adults; 2) anticipated benefits of making vaccine available through emergency use authorization prior to licensure; and 3) robustness of available safety data (including data from experience in older age groups) to inform risk assessment.

Although COVID-19 disease burden is generally lower in younger pediatric age groups compared with adolescents and adults, severe COVID-19 resulting in hospitalization or death does occur in infants and children 6 months to <12 years of age. However, age group-specific risks of COVID-19, considered together with physiological differences between younger pediatric age groups and adults, may present arguments against relying on the same shorter duration of clinical trial safety follow-up to support emergency use authorization (compared to safety follow-up needed to support licensure) as would be acceptable for adolescents. Thus, in considering these age group-specific differences involving benefits and risks, a conclusion of clear and compelling safety and effectiveness to support emergency use authorization may be less certain for younger pediatric age groups than for adolescents and adults.

3. POST-LICENSURE/POST-AUTHORIZATION FOLLOW-UP IN PEDIATRIC POPULATIONS

Pharmacovigilance activities for use under EUA as well as post-licensure include both passive and active surveillance of adverse events. FDA and CDC take a collaborative and complementary approach to reviewing adverse events. Any potential safety signals or other safety concerns identified during the clinical development program will be investigated in post-authorization or post-licensure studies.

The main system for passive safety surveillance is VAERS (Vaccine Adverse Event Reporting System), which is the nation's early warning system for vaccine safety, to which vaccine recipients, caregivers, and healthcare providers can report adverse events at any time after vaccination. For licensed vaccines, healthcare providers and manufacturers are required to report certain adverse events.[19] For COVID-19 vaccines currently being used under EUA, vaccination providers and manufacturers are required to report serious adverse events (irrespective of attribution to vaccination), cases of multisystem inflammatory syndrome in children and adults, and cases of COVID-19 resulting in hospitalization or death. Vaccination providers are also required to report vaccine administration errors, whether or not associated with an adverse event. Reports to VAERS allow for the rapid identification of rare adverse events that might not be apparent in pre-licensure studies. VAERS cannot be used to determine incidence rates of reported adverse events, and because of the lack of an unvaccinated comparison group, VAERS is not designed to assess causality.

Another source of adverse event reports from recipients through passive surveillance of use under EUA is the v-safe program, which is a smartphone-based program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems after vaccination. Reports from vaccine recipients are voluntary. V-safe is complementary to

VAERS and helps detect COVID-19 vaccine safety events in the overall population as well as subpopulations that could be underrepresented in pre-licensure studies.

Active surveillance for safety and effectiveness during use under EUA and post-licensure is accomplished through observational studies conducted in various health care databases, including the Vaccine Safety Datalink (VSD), which collects demographic and health records through a network of 9 participating healthcare organizations across several US regions, networks such as the Sentinel and Biologics Effectiveness and Safety (BEST) programs, which cover more than 100 million persons, and the FDA-CMS partnership (FDA-CMS for persons older than 65 years of age). For general safety evaluation, manufacturers may establish registries or conduct observational studies as post-licensure commitments (PMC). Manufacturers may be required to conduct post-licensure studies to further investigate specific safety concerns.

Post-licensure reporting requirements for manufacturers include expedited reporting of serious and unexpected adverse events as well as periodic safety reports in accordance with 21 CFR 600.80 (postmarketing reporting of adverse experiences). Postmarketing surveillance plans are discussed and agreed with the sponsor during the pre-licensure stage and are finalized according to the specific safety profile and data from each vaccine. During use of a COVID-19 vaccine under EUA, the vaccine manufacturer will conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals for FDA review. Each periodic safety report is required to contain a narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest, newly identified safety concerns in the interval, and actions taken since the last report because of adverse experiences.

4. SUMMARY AND VRBPAC DISCUSSION POINTS

The ongoing COVID-19 pandemic has affected individuals of all ages in the US. Although incidence and severity of disease are generally lower in pediatric populations (especially younger age groups) compared with adults, cases of severe COVID-19 resulting in hospitalization or death have occurred in pediatric populations. Three COVID-19 vaccines are now available under emergency use authorization for use in adults, and emergency use authorization for one of these vaccines has been extended down to 12 years of age based on safety and immunobridging data in adolescents adding to available safety and efficacy data in adults. These and other vaccines are continuing in their development toward licensure in both adult and pediatric populations.

Licensure of COVID-19 vaccines for use in pediatric populations may follow substantial evidence of effectiveness from adequate and well-controlled trials (via immunobridging and/or direct demonstration of clinical endpoint efficacy), plus adequate safety data to support favorable benefit/risk. COVID-19 vaccines could be authorized for emergency use in pediatric populations, depending on benefit/risk considerations that may be different for various age groups. Post-licensure/post-authorization assessment of safety and effectiveness in pediatric populations will include active and passive surveillance by vaccine manufacturers and US government using established mechanisms as well as observational studies.

The VRBPAC will be asked to discuss relevant scientific questions, as described in this briefing document, to data needed to support licensure of COVID-19 vaccines for use in pediatric populations including infants, children and adolescents 6 months to <18 years of age. The

VRBPAC will also be asked to comment on appropriate endpoints and associated statistical success criteria for efficacy trials with formal hypothesis testing to demonstrate COVID-19 vaccine effectiveness in pediatric populations. Finally, the VRBPAC will be asked to discuss circumstances under which emergency use authorization could be considered for age groups within 6 months to <12 years and, in that context, data needed to support benefits of making COVID-19 vaccines available under emergency use authorization and safety data needed to assess risks.

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