# Proposed Framework for Addressing Future COVID-19 Vaccine Strain Composition

## Vaccines and Related Biological Products Advisory Committee Meeting (4/6/2022)

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# Introduction

- FDA and its public health partners will need to make decisions regarding updating the composition of COVID-19 vaccines in the U.S. and potential use of additional booster doses

- VRBPAC will be asked to discuss the process that would be used to update the composition of COVID-19 vaccines in the U.S. and considerations for use of additional booster doses; the discussion will focus on:
  - When should such decisions be made?
  - How should such decisions be made, i.e., what are the criteria?

- Today's discussion is not intended to make a specific recommendation for vaccine composition or for use of additional booster doses

# Background

- Currently authorized and licensed COVID-19 vaccines are based on the SARS-CoV-2 virus that circulated early in the pandemic
- Virus evolution was apparent within months after the beginning of the pandemic and has resulted in emergence of SARS-CoV-2 variants, some of which have become dominant locally (Beta in South Africa) or even globally (Delta, Omicron)
  - Some variants have been more infectious, transmissible, and/or virulent as compared with earlier virus strains
  - Antigenic differences between certain variants and earlier virus strains have resulted in at least partial escape from natural or vaccine-elicited immunity
- Composition of current COVID-19 vaccines may need to be updated to maintain vaccine effectiveness against clinically relevant variants
  - The annual influenza vaccine strain selection process may provide insights for how to consider updating the composition of COVID-19 vaccines

# A Review of the Influenza Vaccine Strain Selection Process

- Each year, any of the previous four influenza vaccine strains may be replaced with a new strain
- Strain changes are necessary to maintain vaccine effectiveness against predominant circulating wild-type strains of influenza virus
- WHO global influenza surveillance continuously monitors evolution and spread of influenza virus strains
- Twice a year, WHO convenes an invitation-only consultation of experts to review and analyze data and to make recommendations for the composition of influenza virus vaccines for the Northern and Southern hemispheres, respectively
- Questions to be answered at each vaccine composition meeting:
  - Are new (drifted or shifted) influenza strains circulating?
  - Are these new viruses spreading in people?
  - Do current vaccines provide protection against the new circulating strains of virus?
  - Can new vaccines with well-matched antigens be manufactured in a timely manner?

# A Review of the Influenza Vaccine Strain Selection Process – 2

- The WHO consultation reviews and analyzes data on the global epidemiology and the genetic and antigenic characteristics of circulating seasonal influenza viruses
- Following review and analysis, the WHO consultation makes recommendations for the composition of influenza virus vaccines
  - February consultation makes recommendations for the next Northern Hemisphere influenza season (vaccine available in ~5-6 months)
  - September consultation makes recommendations for the subsequent Southern Hemisphere influenza season (vaccine available in ~3-4 months)
- WHO notes that "National or regional authorities approve the composition and formulation of vaccines used in each country"
- FDA convenes its Vaccines and Related Biological Products Advisory Committee (VRBPAC) approximately 1 week after the WHO consultation to make recommendations for the composition of influenza vaccines in the U.S.

# A Review of the Influenza Vaccine Strain Selection Process – 3

- Presentations at the VRBPAC influenza strain selection meeting include:
  - Virus surveillance in the U.S.
  - Effectiveness data for most recent vaccines
  - Availability of key vaccine reagents and comments from manufacturers on the practical aspects of changing vaccine composition
- Following review and discussion, the VRBPAC votes on the strains to be included in influenza virus vaccines for the U.S.
- Manufacturers submit a supplement to their license to incorporate the latest vaccine composition recommendation
- Following FDA approval, manufacturers distribute updated vaccine in time for upcoming influenza season

# Why Does this Process Usually Work?

- Predictable seasonality of influenza
- Most influenza vaccines are of similar platforms, and the timelines necessary for updating vaccines are similar for all manufacturers
- Virus genetic and antigenic data used for decision making are generated by WHO Collaborating Centers, Essential Regulatory Laboratories, and other WHO Reference Laboratories
- Animal sera and in vitro data reliably distinguish antigenically different viruses
- Antigenic differences among viruses generally predict differences in immunogenicity and the corresponding clinical responses to vaccines
- Because of the predictive power of in vitro antigenic data and extensive manufacturing experience, new clinical data are not required for an updated influenza vaccine

# When Does the Process Not Work Well?

- Estimates of vaccine effectiveness are approximately 60% for the overall population when the vaccine is well-matched to circulating viruses, but effectiveness is substantially reduced (especially in highly susceptible populations, e.g., elderly) when there is a poor match
- Vaccines that are less well matched to circulating influenza viruses can result from different reasons:
  - Antigenically distinct viruses emerge after recommendations have been made, and these viruses co-circulate or dominate over recommended vaccine viruses
    - 2009 H1N1 pandemic virus (April); 2014 H3N2 drift variant (Feb [1%]; Sep [67%])
  - Manufacturing issues that cannot be resolved in timely manner and that preclude production of a well-matched vaccine
    - Amino acid changes due to egg adaptation; difficulties in deriving a high growth candidate vaccine virus
- Contingency plans are available in situations of severe mismatch
  - Supplemental monovalent A/Taiwan/1/86 H1N1; monovalent 2009 H1N1 pandemic vaccine

# Challenges to Adapting the Influenza Model to COVID-19 Vaccine Strain Composition Decisions

- SARS-CoV-2 variants have not appeared in a predictable seasonal pattern and have not always spread globally
  - Nevertheless, a substantial wave has occurred each of the past two winters
- Multiple types of COVID-19 vaccines are in development, authorized, or licensed
  - Several manufacturers are evaluating vaccines with updated composition (e.g., variant-specific, multivalent, etc.) but clinical trials are ongoing and at various stages of progress
  - Development of modified COVID-19 vaccines by different manufacturers is not currently coordinated with respect to strain composition(s) being evaluated
  - Time needed to manufacture an updated COVID-19 vaccine may differ significantly depending on the vaccine platform, the manufacturer's experience, and the facility capacity

# Challenges to Adapting the Influenza Model to COVID-19 Vaccine Strain Composition Decisions – 2

- Because of limited experience to date, FDA currently requires vaccine-specific clinical safety and effectiveness (immunogenicity) data to support authorization of a modified COVID-19 vaccine from any given manufacturer
- Recent update to Guidance for Industry "Emergency Use Authorization for Vaccines to Prevent COVID-19," Appendix 2: "Evaluation of Vaccines to Address Emerging SARS-CoV-2 Variants"
  - Applicable to strain change modifications of authorized or approved COVID-19 vaccines ("prototype" vaccines) expressing the SARS-CoV-2 S protein
    - Same platform and manufacturing process for prototype and modified vaccines
    - Guidance only covers monovalent modified vaccines, but recommendations could be adapted for evaluation of multivalent vaccines
    - Modified vaccine should be evaluated as primary series and as booster dose(s)
  - Evidence for effectiveness will be derived from immunogenicity data (neutralizing antibody responses) against clinically relevant variants and demonstrated effectiveness of the prototype vaccine
    - Assumes neutralizing antibody to S is a major component of the vaccine protective response

# Challenges to Adapting the Influenza Model to COVID-19 Vaccine Strain Composition Decisions – 3

- Ideally, the process of changing the COVID-19 vaccine would be coordinated globally
- Global coordination may be challenging due to:
  - The unpredictable nature of SARS-CoV-2 evolution
  - Regional differences in VOC circulation or dominance
  - Different regional levels of vaccination coverage and types of vaccines in use
  - Variable timeliness of availability of clinical data for different vaccines to support a need for a modified vaccine
  - Implementing a coordinated global process will likely take some time
- A process for updating the composition of COVID-19 vaccines in the U.S. will need to be flexible, as well as orderly, transparent, and data driven
  - Consideration could be given to scheduling a periodic review of the COVID-19 epidemiology and available clinical data for vaccines against VOC

# Conditions Necessary to Make a Recommendation for Changing COVID-19 Vaccine Strain Composition

- Epidemiology data identifies an antigenically distinct variant(s) that is or will likely become dominant
- Immunogenicity and effectiveness data indicate that current COVID-19 vaccines provide insufficient protection against circulating variant viruses
- Data to justify a recommendation for a strain composition change is available for at least one (and ideally more than one) COVID-19 vaccine
- Vaccine manufacturers have clinical data to support the safety and effectiveness of modified vaccines for their respective products
- Vaccine manufacturers are able to manufacture and deliver a modified vaccine in sufficient quantities, and within a sufficient timeframe, to make an impact

# Some Additional Questions to be Considered in a COVID-19 Vaccine Strain Composition Decision

- Does the available clinical data support changing the strain composition of vaccines currently in use?
  - Should modified vaccines be mono-valent or multi-valent?
  - What strain(s) should be included?
- Does the available clinical data indicate how well a modified vaccine would impact breadth of coverage against circulating and potentially emergent viruses?
  - Are breadth of coverage considerations different for vaccines used as primary series vs. booster doses?

# Some Additional Questions to be Considered in a COVID-19 Vaccine Strain Composition Decision – 2

- How often should the composition of COVID-19 vaccines be reviewed for possible composition update?
  - Yearly, as for influenza? As VOCs appear and become dominant?
  - What contingency plans should be considered if a novel SARS-CoV-2 variant emerges and is not well covered by available vaccines?
- If a strain composition change is recommended, how is a smooth transition to use modified vaccines implemented?
  - Recommendations for seasonal influenza vaccines apply to all vaccines, and vaccines have a dating period that eliminates any potential confusion
- What additional data or experience could expedite the process for COVID-19 vaccine composition changes by limiting or obviating the need for clinical data?

# A Tentative Framework for Considering COVID-19 Vaccine Composition in the U.S.

- The FDA would seek the advice of the VRBPAC to make recommendations for any change in composition of authorized or approved COVID-19 vaccines in the U.S.
  - On a routine basis (TBD), the FDA and VRBPAC will review the epidemiology of circulating SARS-CoV-2 variants in the U.S., the effectiveness of available vaccines in use, and the available clinical data and manufacturing concerns for modified vaccines, in order to determine whether to recommend an updated vaccine for use in the U.S.
  - A collaborative plan including manufacturers, FDA, and other public health agencies, should be developed to provide the necessary clinical data needed for future vaccine composition decisions
  - Contingency plans should be developed to respond to an emerging variant that escapes protection provided by currently available vaccines
- If the WHO does make a COVID-19 vaccine composition recommendation, the FDA and VRBPAC will evaluate whether that recommendation should be implemented for U.S. COVID-19 vaccines, with consideration given to:
  - Epidemiology of circulating SARS-CoV-2 variants in the U.S.
  - Capability of manufacturers of authorized vaccines to implement the recommendation in a timely fashion
  - Availability of clinical data to support safety and effectiveness of recommended modified vaccine

# Considerations for Use of Additional Booster Doses

- A recommendation for an additional booster dose might follow a recommendation for changing COVID-19 vaccine strain composition that occurs as the result of either a scheduled or ad hoc review of COVID-19 epidemiology and vaccine effectiveness
- Even if available data continue to support use of prototype vaccines going forward, periodic use of additional booster doses (e.g., annually, similar to seasonal influenza vaccines) may be needed to maintain adequate immunity
- Recommendations for use and timing of additional booster doses should consider:
  - Goals of vaccination program (e.g., preventing significant morbidity and mortality, as opposed to preventing mild disease, infection, and transmission)
  - In which population(s) additional booster doses are warranted
  - Practical/operational aspects of public health vaccination programs

# Topics for Discussion

Following the open public hearing, the VRBPAC will be asked to discuss and provide input on the following topics (no voting questions):

- What considerations should inform strain composition decisions to ensure that available COVID-19 vaccines continue to meet public health needs, e.g.:
  - Role of VRBPAC and FDA in coordinating strain composition decisions
  - Timelines needed to implement strain composition updates
  - Harmonization of strain composition across available vaccines
- How often should the adequacy of strain composition for available vaccines be assessed?
- What conditions would indicate a need for updated COVID-19 vaccine strain composition, and what data would be needed to support a decision on a strain composition update?
- What considerations should inform the timing and populations for use of additional COVID-19 vaccine booster doses?


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