

Influenza Vaccine Production

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OVERR/CBER/FDA

Regulation of Influenza Vaccines

- Vaccines are regulated by CBER's Office of Vaccines Research and Review (OVRR)
- Authority resides in Section 351 of the Public Health Service Act and the Federal Food, Drug and Cosmetic Act
- The safety, efficacy, purity and potency of these products is assured by thorough review and evaluation of laboratory and clinical data, confirmatory testing, and periodic inspection of manufacturing facilities

Routine Licensing Actions for Annual Influenza Vaccines in the U.S.

- Four licensed inactivated vaccines; one live attenuated
- Each year, any of the previous three vaccine strains may be replaced with a new strain
- Strain changes are based on evaluation of circulating wild-type strains and recommendations of the WHO and VRBPAC
- Submission of a prior approval manufacturing supplement to an existing license is required for annual influenza strain changes
- Clinical data for approval of these annual supplements not required for inactivated flu vaccine

Influenza Strain Selection

- Antigenic drift continuous in influenza A and B viruses
 - Antigenic shift less common but major concern (e.g., H5)
- Vaccine composition must be updated regularly to maintain efficacy which is related to:
 - Potency of vaccine (immunogenicity), e.g., amount of hemagglutinin (HA)
 - Match of the vaccine HA (and possibly NA) with circulating strains
 - First evidence of reduced vaccine effectiveness because of antigenic drift within 2 years after first vaccines licensed in U.S.

Questions to Be Answered for Strain Changes Every Year

- Are new (drifted or shifted) influenza viruses present?
- Are these new viruses spreading in people?
- Do current vaccines induce antibodies against the new viruses (HA)?
- Are strains suitable for vaccines available?

Surveillance and Vaccine Strain Recommendations

- Recommendation for selection of strains to be included in the vaccines depend on:
 - Robustness of the data
 - Accurate typing and characterization of isolates
 - Trending of the data
 - Extent of data
 - Timeliness of the data
 - Timelines for vaccine production are extremely tight and relatively inflexible

Vaccine Strain Recommendations

WHO Global Surveillance



WHO Strain Recommendations for
Northern Hemisphere – mid February



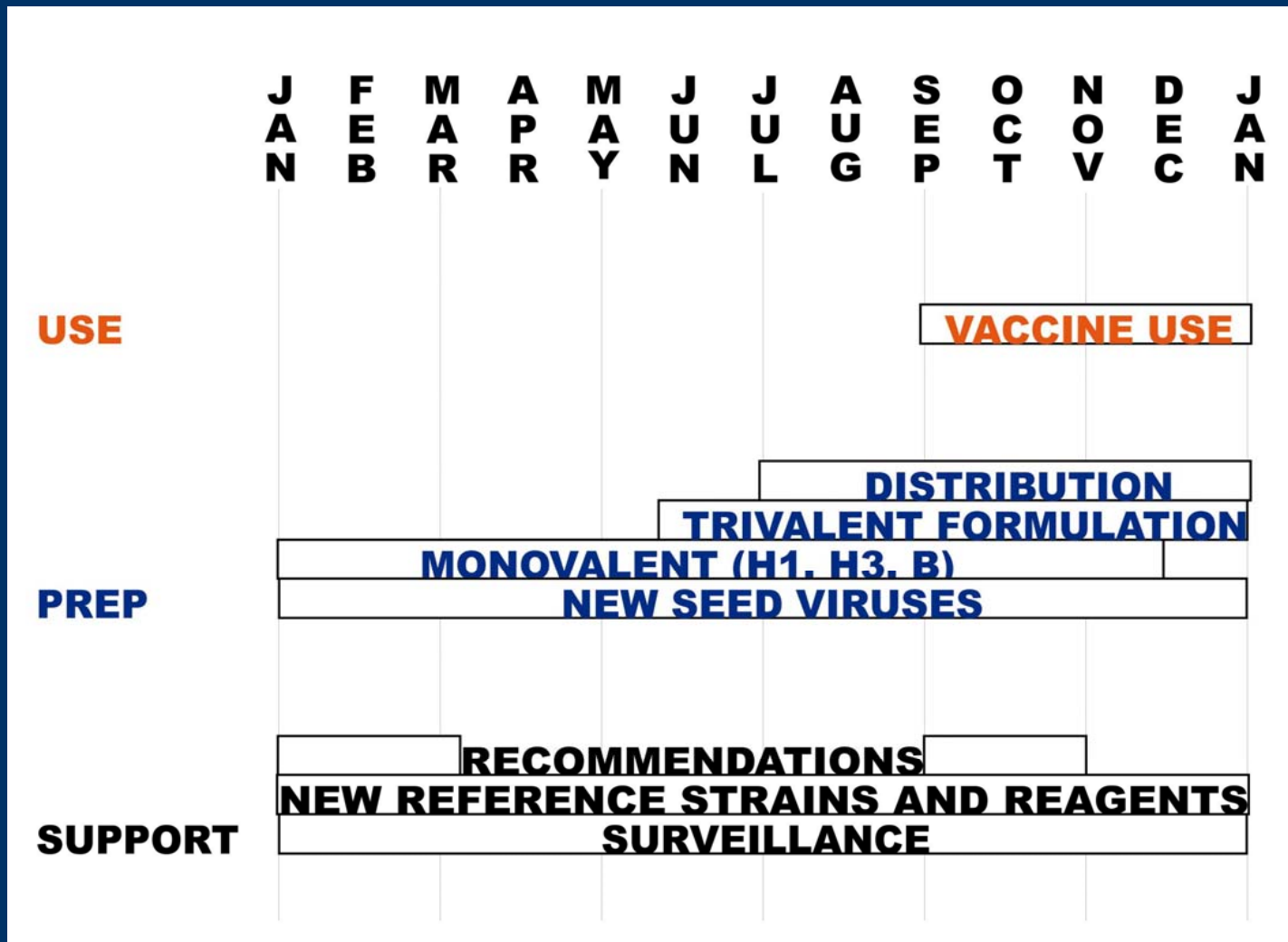
National Regulatory Authorities Recommendations
Vaccines and Related Biological Products Advisory
Committee (VRBPAC) – late February

- Input from CDC (WHO Collaborating Center)
- Department of Defense
- Manufacturers (availability and characteristics of strains under consideration)

Seed Viruses for Manufacturing

- WHO Global Surveillance
 - Provides characterized reference viruses
- WHO Collaborating Centers
 - Provide high growth reassortants
- Manufacturers
 - Develop proprietary seed viruses
- Regulatory Agencies
 - Accept reference viruses and approve seed viruses for use in licensed vaccine preparations

General Timelines for Influenza Vaccine Production



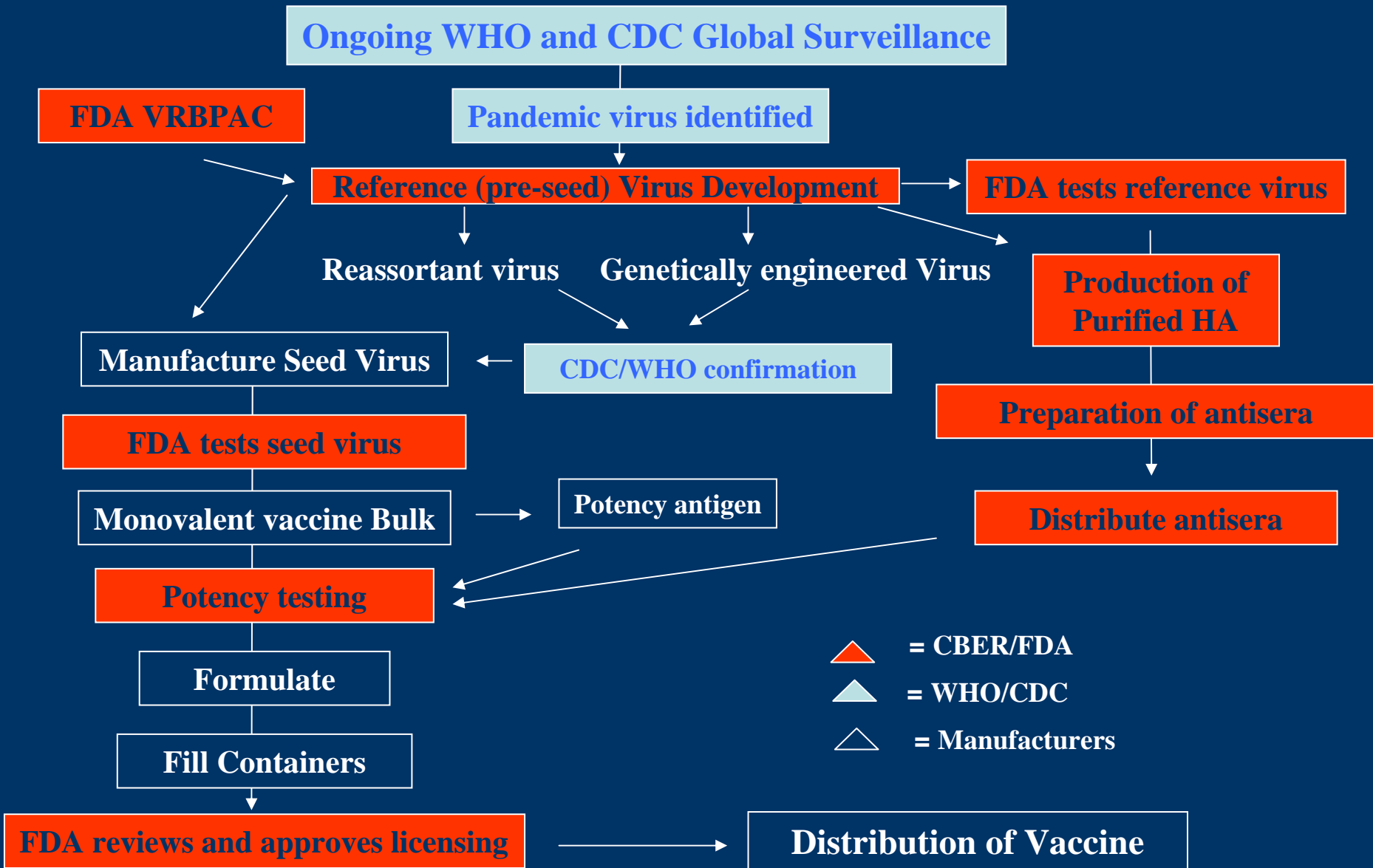
CBER's Annual Influenza Vaccine Program

- Perform serology studies in support of strain selection
- Develop new high growth influenza virus strains for vaccines
- Evaluate manufacturer's influenza viruses prior to vaccine production
- Prepare influenza virus reagents to determine purity and strength of influenza vaccines
 - Distribute to vaccine manufacturers

The Pandemic Influenza Vaccine Challenge

- New strains of influenza can emerge into the human population at any time
 - Natural avian and swine reservoirs
- Emergence of a new influenza will be a global problem
- Timelines for vaccine production relatively fixed and capacity limited
 - Timely identification of pandemic strain critical
- Optimal pandemic vaccine composition, formulation, and schedule unknown
 - Lack of previous exposure make correct strain match essential
- New technologies may be needed to facilitate vaccine manufacturing and immunogenicity
- Regulatory pathways need to be defined in advance to expedite vaccine availability

Production of Inactivated Pandemic Vaccine





Toward a Pandemic Influenza Vaccine

- The regulatory pathway for pandemic vaccines is similar to that of annual influenza vaccine
- CMC and clinical information (both pre- and post licensure) will be required
- FDA's review process will build on existing knowledge of influenza in comparison to the annual vaccine
- Research efforts will focus on facilitating vaccine development, including the evaluation and use of new technologies

Summary

- Influenza vaccines present unique considerations for product development, including accurate strain recommendation
- FDA is working with partners to diversify and strengthen influenza vaccine manufacturing, and providing flexible rapid regulatory pathways
 - Accelerated approval of new vaccines
 - Strain changes to licensed processes
 - Guidance to manufacturers regarding clinical data needed
- Further advance preparation and improvement of strains, reagents, assays and standards is important
- Evaluation of new manufacturing techniques (e.g., non-egg based technologies) and new product technologies (e.g., antigen sparing approaches), are best addressed before a pandemic – key studies are beginning