Influenza Vaccine Manufacturing

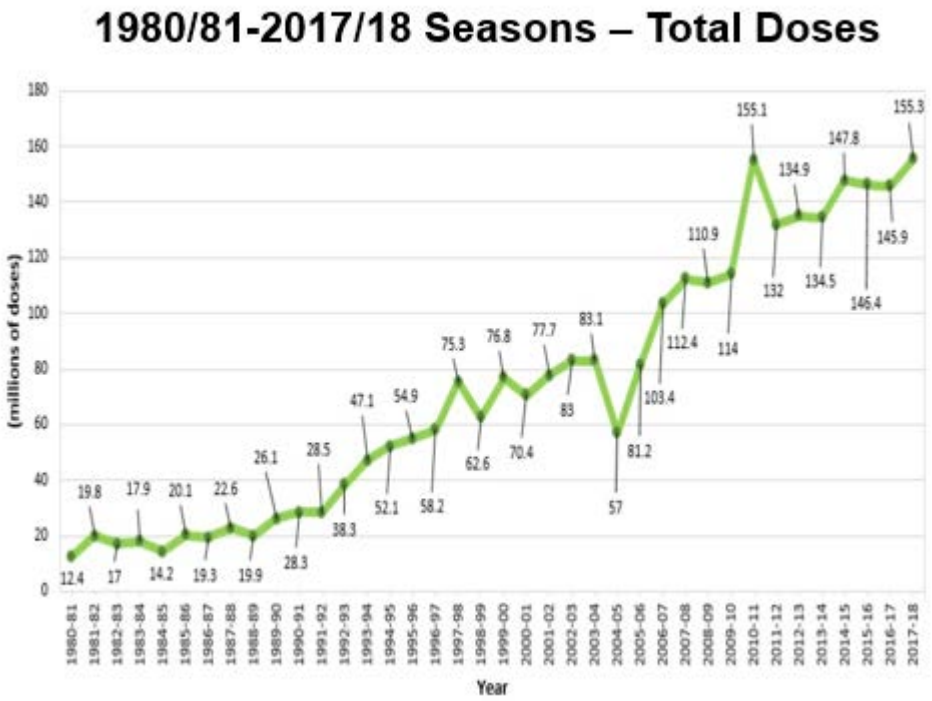
Industry Perspective for 2019-20 Northern Hemisphere Influenza Vaccine Supply

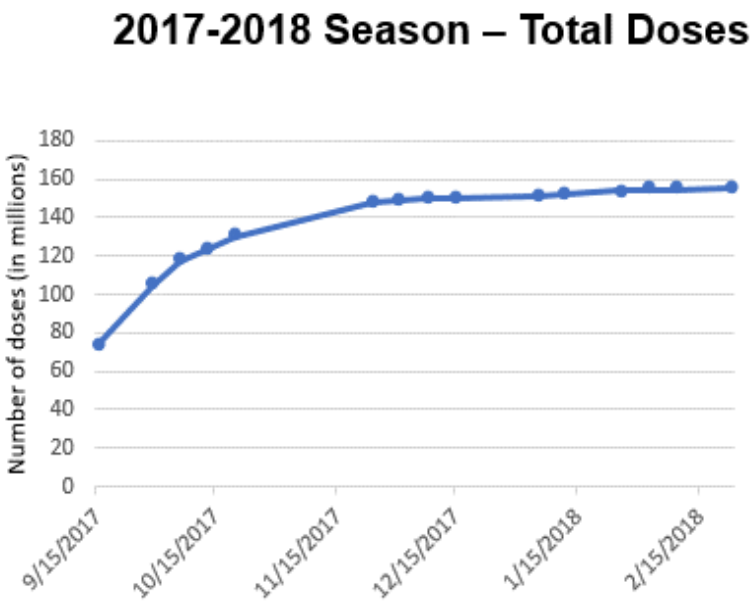
Vaccines and Related Biological Products Advisory Committee

06 March 2019

The FDA CBER requested this annual summary of information from influenza vaccine manufacturers supplying the U.S., for purposes of a general presentation to the VRBPAC. This summary has been prepared from a variety of public sources, and was reviewed by Sanofi Pasteur, AstraZeneca, Seqirus, Protein Sciences and GSK.

US Influenza Vaccine Distribution: 1980-2018

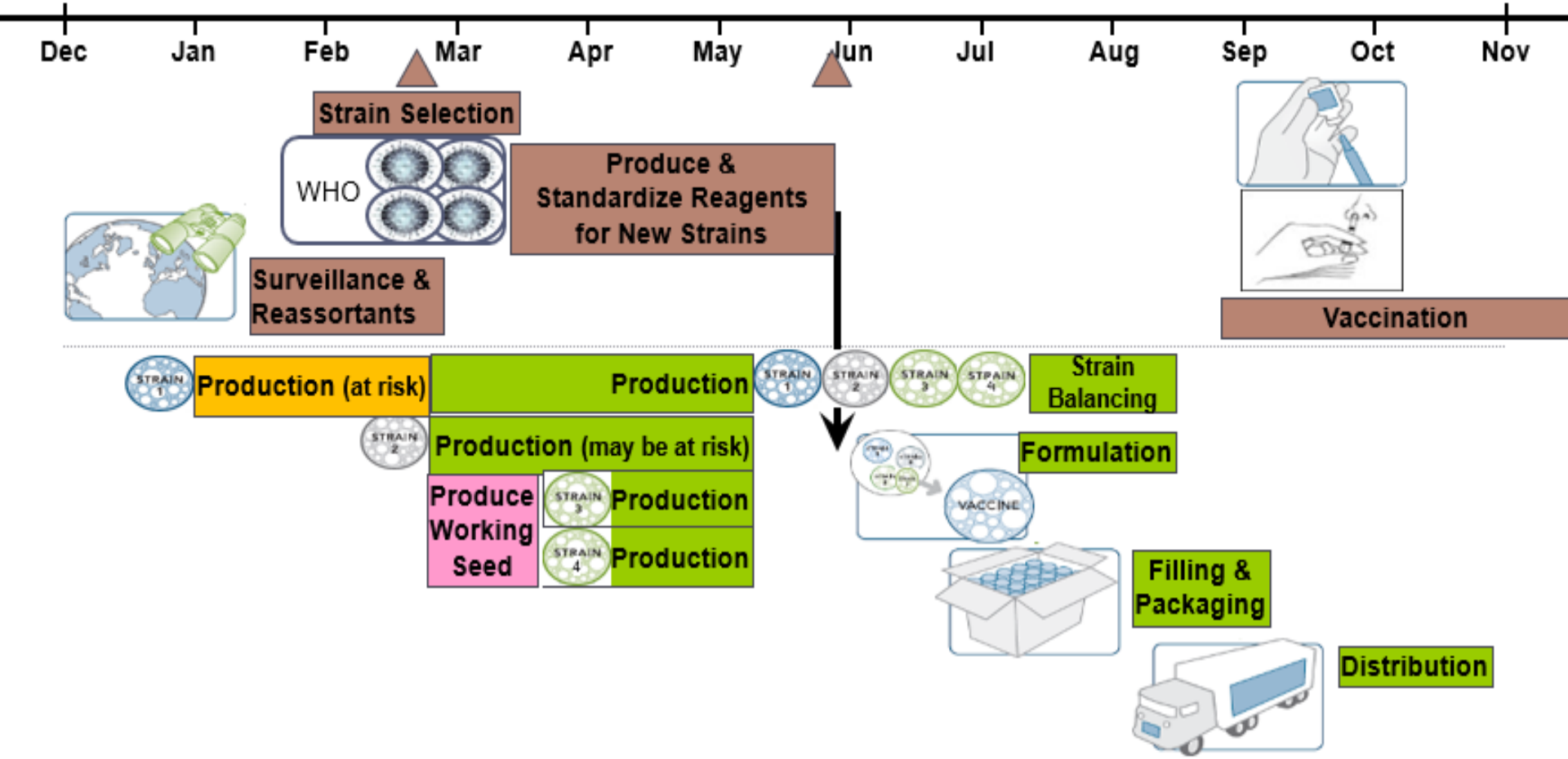




- Vaccine supply requires well-matched strains, sufficient quantities, timely pre-season delivery
- To date (15Feb'19) ≈169.1 million doses distributed in 2018/19 NH season

*Reported to CDC by manufacturers and selected distributors http://www.cdc.gov/flu/professionals/vaccination/vaccinesupply.htm

Annual Influenza Vaccine Manufacturing Timeline for NH Supply



Influenza Vaccine Manufacturing Critical Factors

- Global timing of strain selection ensures large vaccine supply
  - Available time to manufacture influenza vaccine is determined by
    - Need to distribute & administer vaccine well before the peak season
    - Availability of candidate vaccine viruses for vaccine suppliers
  - To ensure timely availability of influenza vaccine, manufacturing of at least one strain starts at risk before VRBPAC recommendations
  - Antigen yields from the least productive vaccine virus strain are the limiting factor and determine the number of vaccine doses supplied

WHO 2019-20 NH Season Flu Recommendation

Influenza

Recommended composition of influenza virus vaccines for use in the 2019-2020 northern hemisphere influenza season

21 February 2019

It is recommended that egg based quadrivalent vaccines for use in the 2019-2020 northern hemisphere influenza season contain the following:

- an A/Brisbane/02/2018 (H1N1)pdm09-like virus;
- an A(H3N2) virus to be announced on 21 March 2019*;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

It is recommended that the influenza B virus component of trivalent vaccines for use in the 2019-2020 northern hemisphere influenza season be a B/Colorado/06/2017-like virus of the B/Victoria/2/87-lineage.

* In light of recent changes in the proportions of genetically and antigenically diverse A(H3N2) viruses, the recommendation for the A(H3N2) component has been postponed.

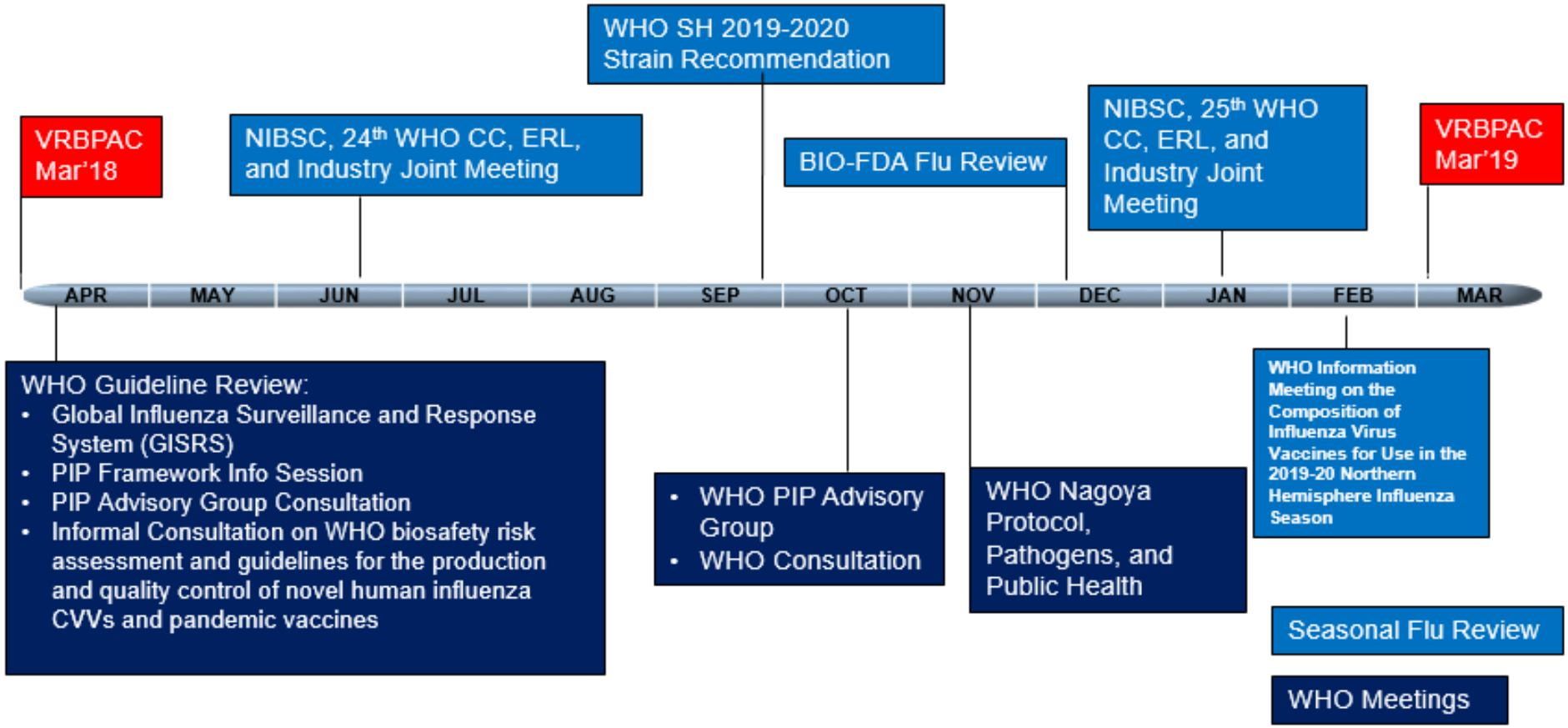
Additional Critical Factors

- Availability of potency test reagents
  - Complex process to prepare and standardize potency reagents for new strains
  - Linked to global timing of strain selection for new strains
  - Availability of calibrated reagents determines start of influenza vaccine formulation

Manufacturers Preparations for Upcoming NH 2019/20 Season

- Tracking surveillance data through summaries of internal WHO TCs that include a table listing viruses of interest, NIBSC meetings, BIO/FDA meeting and discussions with WHO Collaborating Centers.
- Regular reviews of websites such as WHO FluUpdate and Flunet, CDC FluView and GISAID.
- Tracking availability of CVVs for manufacturing through WHO chaired Technical TCs and updates from WHO CCs that have been ongoing since the WHO SH recommendation (Sep 2018).
- A spreadsheet of viruses of interest and stage of preparation of CVVs is now regularly shared with manufacturers providing timely updates on development status. (Spreadsheet at times does not reflect current status of preparation and testing for release.)

Industry Closely Engage with WHO and US Agencies at Multiple Forums



- Illustrates close, collaborative, working relationship to resolve issues
- Improve influenza vaccine supply, pandemic preparedness, future strategy
- Key decisions made at multiple influenza forums, with broad global impact

Principal Egg- Isolate CVV Influenza Strains Evaluated for NH 2019/20

Virus Type	Egg-Isolate CVV
A(H1N1) pdm09	~~Michigan/45/2015~~
	~~Scotland/P2/2015~~
	~~Lisboa/32/2015~~
	~~Singapore/GP1908/2015~~
A/H3N2	~~Switzerland/8060/2017~~
	~~Brisbane/1/2018 & Brisbane/192/2017~~
	~~Rhode Island/01/2018~~
B/Victoria	Colorado/06/2017
	Maryland/15/2016
B/Yamagata	Brisbane/9/2014
	Utah/09/2014

Principal Cell-Isolate CVV Influenza Strains Evaluated for NH 2019/20

Virus Subtype	Cell-Isolate CVV
A(H1N1)	A/Singapore/GP1908/2015 (egg)
	A/Singapore/TT1384/2016
	A/Idaho/07/2018
A(H3N2)	A/North Carolina/04/2016
	A/Canberra/7/2016
B/Victoria	B/Iowa/06/2017
B/Yamagata	B/Singapore/INFTT-16-0610/2016
	B/Singapore/INFKK-16-0569/2016

Nagoya Protocol Update: Background & Impact

- Developed from access-and-benefit sharing discussions at the Convention on Biodiversity (CBD), adopted in 2010 and came in to force October 2014 to:
  - Ensure access to genetic resources and related traditional knowledge for potential use
  - Ensure users and providers of genetic resources and related traditional knowledge agree on fair and equitable sharing of benefits arising from their use. Benefits may be monetary or non-monetary.
- Jan'19: 116 countries have ratified the NP and entered it into force.
- Seasonal influenza virus strain R&D is in scope of the CBD/Nagoya Protocol (pandemic appears exempt under NP Article 4: SII / Emergency response terms)
- Pathogens included hence time (~ 3 months) required to formalize legal benefit sharing arrangements to use the genetic resources from each source NP participating country.
- Through 2019, industry will attend consultations/meetings with CBD, WHO &/or at the WHA to support NP-public health discussions to facilitate exempting influenza from Member State NP legislation impacting pathogen sharing and use, that risk significantly delaying supply of vaccine to patients.
- ***Manufacturers appreciate the efforts, but remain concerned about the impact to seasonal influenza vaccine supply for the U.S. market.***

SII, Specialised International Instrument

Examples of Nagoya Protocol Impact

There are now several examples of delays in supply of seasonal influenza viruses to WHO CC's or approval to use viruses due to implementation of the Nagoya Protocol (NP):

- The WHO GISRS National Influenza Centre (NIC) in Vietnam did not share influenza viruses as part of the global surveillance program in time for the SH2019 WHO VCM because PICs & MATs under NP had not been agreed. This has now been resolved.
- The NIC in Brazil is not supplying viruses to CDC as part of the surveillance program until the PIC and MAT under NP have been agreed. CDC is working to resolve this and this is still ongoing
- For the 2019/2020 influenza vaccine two strains originate from countries that have signed the Nagoya Protocol and reassortants are being prepared for both of them.
  - A/Netherlands/10260/2018 (H3N2)
  - A/Switzerland/3330/2017 (H1N1)pdm09

Additional Examples of Nagoya Protocol Impact

- Switzerland has passed NP legislation requiring clarification by the Francis Crick Institute from the Swiss competent authority for NP (FOEN) on what was required
  - After an initial delay (~ 3 months), a tracking reference number was allocated for H3N2 A/Switzerland/8060/17, a WHO recommended strain for the SH2019 season
  - Switzerland does not require access benefits for use of their influenza viruses but will track use of Swiss genetic resources for up to 10 years
  - Companies planning to use a A/Switzerland virus are required to notify FOEN prior to commercial use of the strain

- NIBSC could not supply H3N2 A/Bretagne/1565/17 reassortant to manufacturers until clarification had been received from France about their NP legal requirements
  - The Francis Crick Institute spent 3 months getting clarification from the Pasteur Institute before being informed that France intends to pass legislation to exclude human pathogens from NP

Concluding Comments

- Timely strain selection and vaccine supply requires close collaboration between multiple stakeholders to ensure sufficient provision of vaccine each season.
- 2019-2020 season manufacture preparedness is ongoing however there is the potential for delay in supply due to the postponement of the recommendation of the A (H3N2) strain. Improvements need to be implemented to mitigate later strain recommendations.
- Adherence to the Nagoya Protocol could result in a delay in influenza vaccine supply; influenza vaccine industry is going to collaborate with WHO and CBD to facilitate mitigating this risk.
- Maintain public confidence in vaccination.

Thank you for your attention