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Influenza Vaccine Manufacturing

Industry Perspective:

Challenges and Opportunities for Vaccine Strain Composition with the Reduced Public Health Threat from Influenza B/Yamagata Lineage Viruses

Vaccines and Related Biological Products

Advisory Committee

05 October 2023

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Global Senior Expert Medical Strategy

Sanofi Vaccines (Informed by consultation with Influenza Vaccine Manufacturers)

CBER requested this summary of information from U.S. licensed influenza vaccine manufacturers for purposes of a general presentation to VRBPAC. This summary has been prepared from a variety of public sources, and was reviewed by Sanofi, AstraZeneca, GSK and CSL Seqirus.

Presenter Disclosure Statement

- Employee of Sanofi and own shares in the company

Public Health Partnership & Commitment to Patients

- **To maintain confidence in vaccines and ensure a stable and predictable environment for flu vaccine manufacturing, supply and implementation, we request a scientific framework to guide the proposed removal of the B/Yamagata strain. Acknowledging the period of low/absent circulation, we are willing to develop this in parallel to preparing for the transition to TIV.**
  - We value partnership and collaboration with all public health authorities.
  - We have a unified commitment to accessible and timely delivery of influenza vaccines to reduce the burden of influenza disease worldwide.
  - We strongly desire to continue building vaccine confidence and trust worldwide, which directly impacts global public health.
  - We are aligned with transitioning all licensed vaccines in the same timeframe to minimize confusion and impact to vaccine confidence starting with the 2025/2026 NH season.

Considerations During Transition:

- There are benefits in providing a scientific framework that supports a recommendation to ensure we meet public expectations for transparency around public health decisions.
- Acknowledgement that QIV and TIV have similar safety (reactogenicity and tolerability) profiles.
- Risk of B/Yamagata re-emergence via viral escape during manufacturing or a LAIV reassortment event is negligible.
- Enhanced surveillance should be continued to monitor for re-emergence of B/Yamagata in circulation.

We hear the ongoing concerns regarding B/Yamagata. Through this presentation we are looking for cross-sector partnership to achieve an organized approach that protects public health and confidence in vaccines.

"…the question is not 'if', but 'when' to exclude / to remove the B/Yam composition in the seasonal vaccines"

"…the action of inclusion or exclusion of B/Yam in seasonal vaccines needs to be taken in an organized approach involving public and private sectors including surveillance, regulatory agencies,…"

– Dr. W. Zhang – ESWI – 20 September 2023

Transition Timelines Will Vary Based on Global Regulatory Environments

Following the WHO/MHRA meeting, 13 IVS member companies responded to a questionnaire that aimed to highlight realistic steps that companies will work on to make a transition to TIV.

- Total number of TIV licenses needing re-activation or submission / re-submission globally = **355**
- Number of variations needed to update TIV licenses = **1,490**
- Number of countries (including US) requiring new regulatory submissions to old TIV licenses to update CMC and quality data aligned with current quality standards **= 174**
- The following timeframes are estimates based on standard global timelines:
  - **Up to 36 months** for Region of Americas (AMR), European Region (EUR), African Region (AFR), and Western Pacific Region (WPR)
  - **Up to 48 months** for South East Asian Region (SEAR) and Eastern Mediterranean Region (EMR)

A clear and aligned regulatory framework is needed to enable the transition, and we look forward to consulting with authorities to develop this.

Global Transition Timelines – Southern Hemisphere 2024 & 2025

Industry appreciates the critical role VRBPAC has in recommending the influenza strains that manufacturers will use in supplying SH markets.

We ask VRBPAC to make strain recommendations for both TIV and QIV, so that SH countries can avoid potential supply shortages. Industry recognizes that many National Regulatory Agencies transition timelines will vary based on individual regulatory environments.

- While TIV licenses are only "inactivated" in the US, in many other countries the TIV licenses are either "withdrawn" or were never granted, thereby requiring a full New Marketing Application to be submitted, reviewed, and approved.

- Considering the IFPMA IVS survey results, international markets may need time to adopt the regulatory framework to support TIV, which might adversely impact supply.

- There are many SH countries that rely on CBER (as their reference authority) for product release.

In conclusion, we ask VRBPAC to recommend strains for both TIV and QIV formulations for SH 2024 and SH 2025 while manufacturers work with dozens of NRAs globally on the required regulatory processes and scenarios to assist them in transitioning to TIV.

Transition Timelines – Northern Hemisphere 2025/2026

There is a significant regulatory burden and risk to US supply to transition to TIV NH 2024/2025. There are important manufacturing changes that have occurred since TIV was last distributed in the US, and these changes require dialogue between individual manufacturers and CBER. Currently, there is no clear regulatory framework for reactivation of TIV shared across manufacturers.

Based on our analysis, we propose a transition starting in NH 2025/2026, which will enable essential collaboration with CBER to take place.

Since TIV products were discontinued in the US and internationally, many changes have occurred in QIV manufacturing, infrastructure, quality, testing, stability, container closure, and packaging (presentation) of influenza vaccines. These changes have not been implemented for TIV.

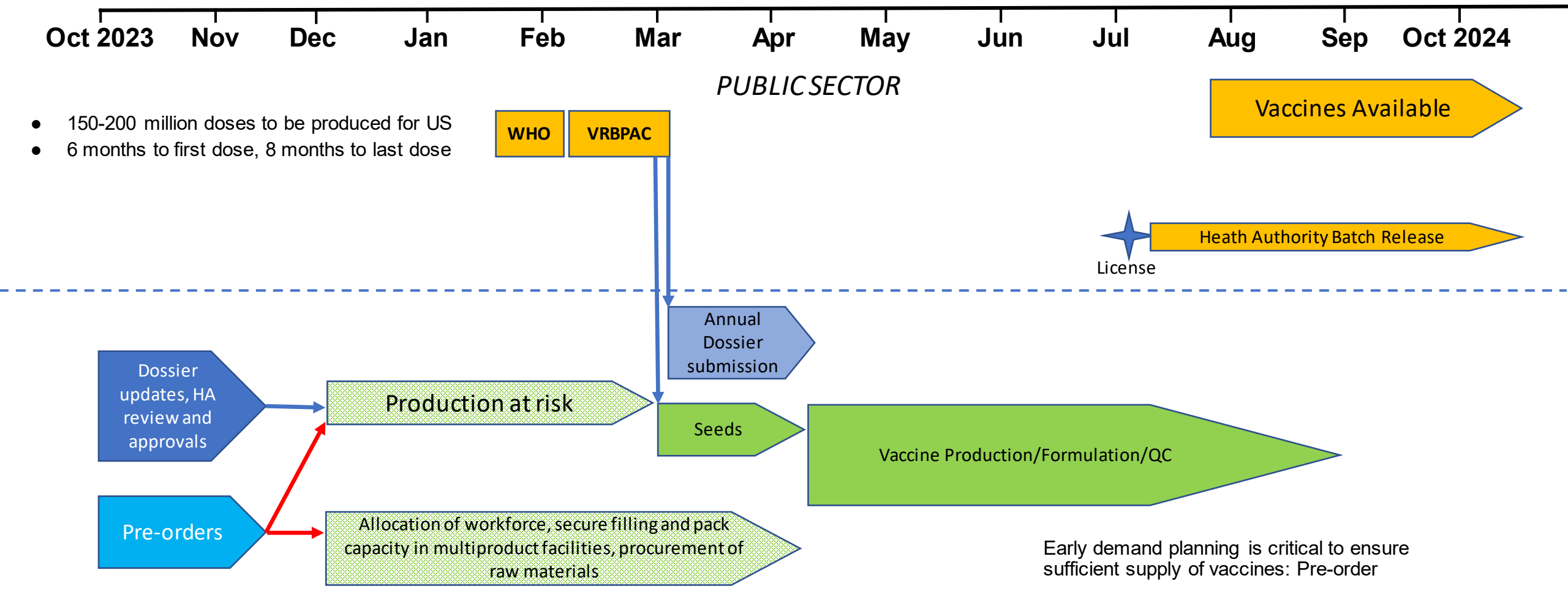
Examples Include:

- For some products / presentations, a TIV formulation was never licensed in the US.
- Manufacturing facilities across multiple companies including external partners have been built and brought online for QIV, but TIV was never manufactured in these facilities.
    - End-to-end manufacturing including quality and validation in many sites are QIV-specific and will need to be re-validated and submitted for TIV.
- Technology transfers to health authorities for TIV manufacturing methods related to TIV release will take 9-18 months.
- At the time of VRBPAC discussion for NH 2024/2025, most supply orders have already been placed by customers.

In conclusion, Industry will continue to work collaboratively and diligently with the FDA and other global regulatory bodies to assess this transition. We feel strongly that VRBPAC should continue with both TIV and QIV strain recommendations until the NH 2025/2026 strain selection in the US, anticipating all TIV regulatory requirements will be approved.

See timeline on next slide illustration.

Annual Influenza Vaccine Manufacturing Timeline for US Supply
NH 2024/2025 QIV Campaign Already Underway



- 150-200 million doses to be produced for US
- 6 months to first dose, 8 months to last dose

Early demand planning is critical to ensure sufficient supply of vaccines: Pre-order

Production at risk before VRBPAC is critical to ensure enough doses are available and production cost are lowered because of better use of capacity

Exploring Development of new Quadrivalent Vaccines

- Industry is open to developing improved QIV formulations to address the burden of influenza, improve protection against currently circulating strains, and improve public health.
  - Tied to enhanced surveillance globally
  - Explore the best options with scientific experts
  - Consider 3 A Strains and 1 B Strain
    - Allow for regulatory flexibility in QIV formulations based on unmet medical need

- We will partner across multiple disciplines: epidemiology, virology, immunology, experts in vaccine design, and public health and regulatory authorities.

The potential to transition to new QIV can be achieved in a timely manner if significant development is undertaken and if there is partnership with regulators to align on requirements.

Conclusion

To maintain confidence in vaccines and ensure a stable and predictable environment for flu vaccine manufacturing, supply and implementation, we ask for a scientific framework to guide the proposed removal of the B/Yamagata strain. Acknowledging the period of low/absent circulation, we are willing to develop this in parallel to preparing for the transition to TIV.

- We are dedicated to **improving public health, influenza vaccine confidence, vaccine supply** and **coverage rates** in the US / globally.
- The potential transition to TIV will require close collaboration with CBER and many other regulatory agencies worldwide to re-activate or re-submit **>300 TIV licenses**, submit nearly **1500 variations**, and update quality data in **174 countries**.
- For **SH 2024 and SH 2025**, **we request VRBPAC recommend strains for both QIV and TIV formulations** as we work efficiently with regulatory agencies and health officials worldwide.
- Given the lead time required for seasonal influenza vaccine manufacturing, contracting, and distribution in the US, **we request that VRBPAC continues with both TIV and QIV strain recommendations until the NH 2025/2026** season, anticipating all TIV regulatory requirements will be approved.
- We plan to explore **improved QIV formulations** to improve protection against currently circulating strains seeking collaboration with the regulatory agencies and vaccine experts.

Thank You