

# COVAX

## Multivalent COVID vaccines to help address emergence of variants: CMC and Clinical implications

Combined Manufacturing and Clinical Development SWAT Team | Wednesday April 14, 2021

CEPI



unicef 

# Meeting Norms and Recording Disclaimer

- Throughout the workshop, please ask questions in the “Q&A” function. If you see that your question is already asked, you can “like” the question in the “Q&A” function.
- This workshop will be recorded. Please be mindful of the diverse audience attending the meeting when participating in open discussions.

# Agenda

Introduction		
10 min	Introductions, meeting overview and rules	Ajoy Chakrabarti, BMGF
15 min	Current thinking: regulatory expectations for variant vaccines	Dean Smith & Catherine Njue, Health Canada
Manufacturing case studies		
20min	Ebola multicistronic vectors	Hubertus Hochrein, Bavarian Nordic
20 min	Challenges of developing a multivalent vaccine for the global market: Gardasil®9	Paula Annunziato & Dicky Abraham, Merck
20 min	Introducing new flu strain and challenges with multivalent vaccines	Beverly Taylor, Seqirus
5 min	Break	
Clinical case studies		
10 min	Introduction	Jakob Cramer, CEPI
10 min	Immunological perspectives	Arnaud Didierlaurent, University of Geneva
15 min	Takeda bivalent norovirus vaccine	Jim Sherwood, Takeda
15 min	Sanofi TIV to QIV influenza vaccine	Kevin Yin and Sandrine Samson, Sanofi
20 min	Moderna COVID-19 vaccines	Darin Edwards, Brett Leav, and Carla Vinals, Moderna
Concluding Remarks and Wrap-up		
10 min	WHO support to regulatory preparedness	David Wood, WHO
10 min	Meeting close and discussion	Jakob Cramer, CEPI

# Introduction

- Addressing the variants will impact development activities related to COVID-19 vaccines for the foreseeable future
- There have been multiple workshops addressing how to introduce a modified or new vaccine to address variants. Today we are focused on **multivalent** vaccines (containing for example an antigen against the prototype strain as well as an antigen directed against a variant) and the lessons learned by others when developing such multivalent vaccines.
- Joint Workshop between the CMC and Clinical SWAT teams has several potential benefits:
  - Highlight the interrelated nature of Clinical and CMC efforts
  - Cross-over learning opportunity to understand how issues from one area impacts the other
- Three major **CMC Themes** for vaccine candidates that cover multiple COVID-19 variants:
  - Impact on potency assays and setting release specifications
  - Impact on formulation and stability
  - Difference between multiple DS that are blended together versus multiple antigens in a single DS
- Three major **Clinical Themes**:
  - Risk of immunological interference. Demonstrate the immunological response to the first antigen is undeterred by the addition of the additional type(s).
  - How to benchmark the response to the new antigen against the response of the prototype vaccine antigen.
  - Safety: the impact of potentially increased antigen amount versus the risk of reduced-dosing failing non-inferiority.

# Current regulatory thinking on multivalent vaccines: Nimble regulation during a pandemic

COVAX Workshop:  
Multivalent COVID-19 vaccines to help address emergence of variants:  
CMC and Clinical implications  
April 14, 2021

Biologic and Radiopharmaceutical Drugs Directorate  
Health Canada  
Dean Smith & Catherine Njue



# Context

- Several prototype COVID-19 products with moderate to high vaccine efficacy have been developed, evaluated in large placebo controlled randomised clinical trials (RCT), authorised and are being deployed in record time
- These prototype vaccines are based on monovalent full-length SARS-CoV-2 original strain Spike(S) protein, native or pre-fusion stabilized
- While longer term characterization of multivalent COVID-19 based vaccines may be prudent, for the rapid development of VOC adapted vaccines, developers should be aware of the potential for additional CMC and clinical challenges with multivalent vaccines against S and other antigens, when broadly neutralizing monovalent adapted VOC S designs may be possible

# Outline: CMC Considerations

- CMC Development
  - General considerations
  - Single antigen DS requiring blending
  - Multiple antigen in single DS
  - VOC Adapted antigen for authorised and new vaccines
- Setting specifications
  - General considerations
  - Dose ranging studies to support specifications
  - Potential complexities with multivalent vaccines

# CMC Development

## General considerations:

- CMC characterization and QC for vaccine antigens in a multivalent vaccine same as that for monovalent, with the additional consideration of antigen interference in the QC assays (e.g., ID, potency and potentially other CQA).
- **Single antigen DS requiring blending:**
  - Permits more direct control specific antigen additions to DP
  - Simplifies the characterization of antigen interference in QC assays, as well as the characterization of potential antigen competition in pre-clinical and clinical studies
  - Requires multiple production runs for DP, and antigen assay specificity in the DP is still required at release and during stability testing



# CMC Development

- **Multiple antigens in a single DS:**
  - Control of specific antigen content in a single expression cassette more complex and less flexible
  - Single production run to produce DP, but same assay specificity requirements at DS and DP
  - Will still require monovalent antigen production during development to characterize antigen QC assays and potentially antigen completion in pre-clinical and clinical studies
  
- **VOC Adapted antigen design:**
  - VOC adapted antigen can be consideration for authorized vaccines, as well as products still in development for both mono and multivalent vaccines
  - **Note:** A demonstration of the added CMC (or clinical) value for all vaccine components, including additional antigens, is generally required

# Setting specifications with multivalent vaccines

- Generally, specifications must be based on characteristics of vaccine lots demonstrated to be safe and effective in clinical studies or through clinical experience (i.e., clinically related/patient-centric specifications)
- Dose ranging studies characterizing NAb and CMI can be as important for setting specifications as there are to determine the target clinical dose in Phase III. Can be essential to support a product through authorization, if clinical lot potency is challenging to maintain through commercial scale up. Also “protects” specifications post-authorization.
- Potential complexity with release/end of shelf-life specifications with multivalent vaccines and differing rates of potency decline between multiple antigens

# Outline: Clinical Considerations

- Clinical Development
- Need for Dose Finding Studies
- Study Designs to Assess Immune Response
- Vaccines Still Under Development

# Clinical Development

- Clinical development program will vary for proposed multivalent vaccines and a distinction should be made between:
  - Multivalent vaccines based on an authorized platform with clear demonstration of efficacy based on a clinical disease endpoint versus
  - Multivalent vaccines based on platforms which are not yet authorized

# Dose Finding Studies

- For COVID-19 vaccines which have already been authorised:
  - the generation of a bi- or multivalent vaccine will likely necessitate additional immunogenicity studies to define the appropriate dose for each sequence
  - Hence, properly designed dose finding studies to determine the optimal dose for each sequence should be conducted

# Dose Finding Studies

- Such studies will not only provide important dose-finding information but also safety information
- The design of such studies should be discussed early with regulators

# Assessing Immune Response

- Once the optimal dose for each sequence has been determined:
  - Studies will also be needed to investigate whether the addition of a second (or subsequent) sequence(s) does not result in an inferior immune response to vaccines with a single sequence
  - The reactogenicity of the multivalent vaccine relative to the single sequence vaccine should also be evaluated

# Assessing Immune Response

- This will necessitate the need for properly designed non-inferiority studies
- The study population, endpoints and non-inferiority margins selected should be justified
- The number of subjects enrolled in the study should be clearly justified based on the design and objectives of the study



# Vaccines Still Under Development

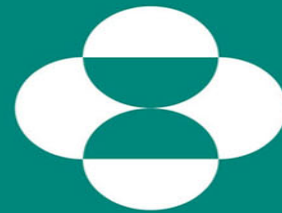
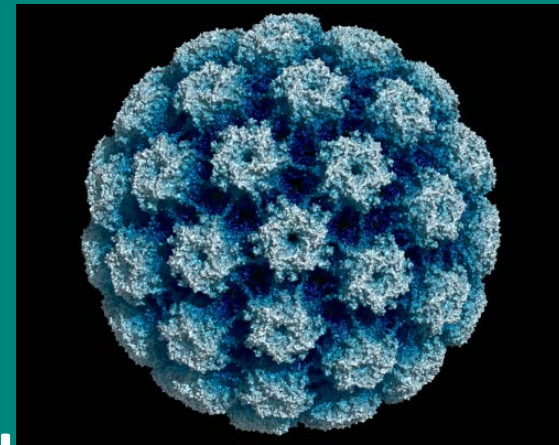
- For multivalent vaccines based on platforms which are not yet authorized:
  - Clinical development plans will depend on the stage of development including available data on immunogenicity, safety and efficacy
  - It is best that such plans are discussed early with regulatory agencies

**Thank-You!**

**Questions?**

**Placeholder: Ebola multicistronic vectors**

# CHALLENGES OF DEVELOPING A MULTIVALENT VACCINE FOR THE GLOBAL MARKET: GARDASIL<sup>®</sup>9



14-April-2021

Dicky Abraham, Distinguished Scientist, Global Vaccines, Merck Manufacturing Division

Paula Annunziato, Vice President, Vaccines Global Clinical Development

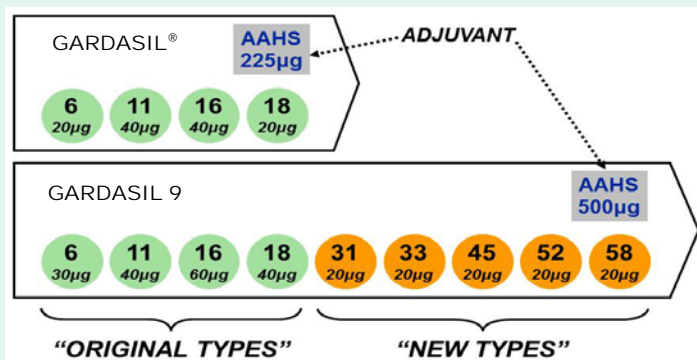


# Clinical Aspects



# GARDASIL<sup>®</sup> 9

## Composition of GARDASIL 9<sup>1,4</sup>



## Impact of Adding 5 HPV Types<sup>2-4</sup>

AAHS=amorphous aluminum hydroxyphosphate sulfate.

Type of Lesion	GARDASIL 9 Types Contribution	GARDASIL <sup>®</sup> Types Contribution	Contribution of HPV Types 31/33/45/52/58
Cervical Cancer*	90%	70%	20%
CIN2/3**	80%	50%	30%
CIN1**	50-60%	30-35%	20-25%

\* Based on de Sanjose et al. 2010 and Serrano et al. 2012  
 \*\* Based on Joura et al. 2014

## Overview of Clinical Program<sup>4-6</sup>

### P001, phase 3 safety and efficacy study (~14,000 subjects)<sup>4</sup>

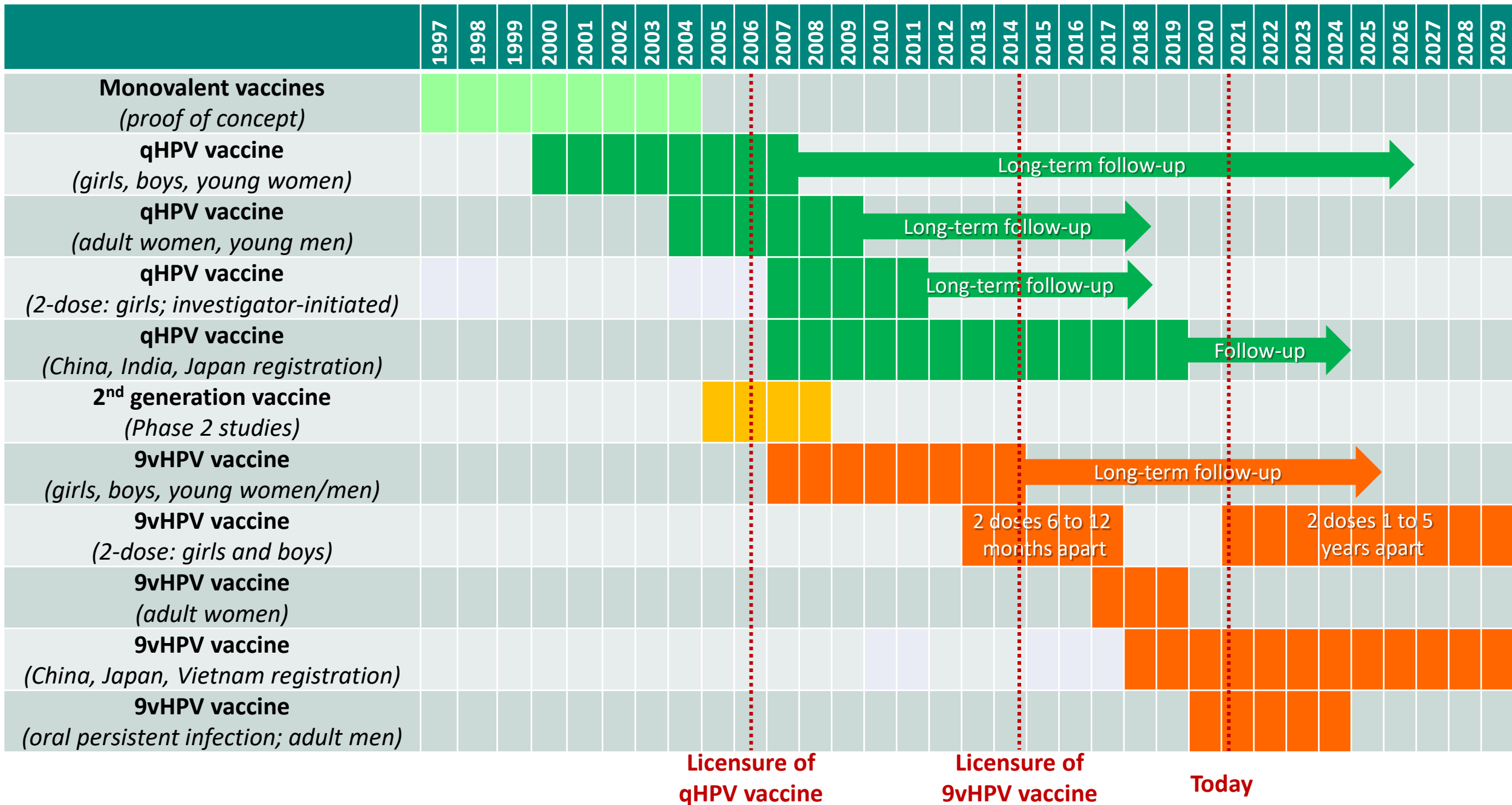
- Clinical efficacy for new types and immunobridging to original types in 16-26-year-old women
- Active comparator GARDASIL<sup>®</sup>
- Immunobridging from GARDASIL to GARDASIL 9
- All primary and secondary hypotheses were met

### Ten phase 3 safety and immunogenicity studies (>12,500 subjects)

- Immunobridging from women 16-26 years of age (3 doses) to girls and boys 9-15 years of age (2- or 3-doses), men 16-26 years of age (3 doses) and women 27-45 years of age (3 doses)
- Immunobridging from GARDASIL to GARDASIL 9 (girls 9-15 years of age, men 16-26 years of age)
- Concomitant use (Menactra, Adacel, Repevax)
- Prior recipients of GARDASIL<sup>®</sup>
- Manufacturing lot consistency
- All primary and secondary hypotheses were met

1. Luxembourg A et al. *Contemp Clin Trials*. 2015;42:18–25. 2. de Sanjose S et al. *Lancet Oncol*. 2010;11:1048–1056. 3. Serrano B et al. *Infect Agent Cancer*. 2012;7:38. 4. Joura EA et al. *N Engl J Med*. 2015;372:711–723. 5. Huh WK et al. *Lancet*. 2017;390:2143–2159. 6. Luxembourg A and Moeller E. *Expert Rev Vaccines* 2017;16:1119-1139.





Licensure of qHPV vaccine

Licensure of 9vHPV vaccine

Today

# The Journey Continues - Regulatory and Recommendation Updates

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Gardasil approved in >130 countries; Gardasil 9 approved in >80 countries

- Examples of recent regulatory approvals:
  - Gardasil 9 approval for females 16-26 years in China (2018)
  - Gardasil 9 mid-adult indication in US (2018)
  - Gardasil 9 oropharyngeal and other head and neck cancer indication in US (2020)
  - Silgard 9 approval in Japan (2020)
  - Gardasil female 9-19 years indication in China (2020)
  - Gardasil male  $\geq 9$  years indication in Japan (2020)

>80 countries with HPV vaccine in National Immunization Program

- Examples of recent recommendations
  - Gender neutral vaccination in EU countries (2018-2019)
  - Mid-adults in US (2019)

Increased interest in HPV vaccination

- HPV disease elimination has been a goal for WHO and certain countries since 2018
- Supply constraint due to sharp increase in demand for Gardasil/Gardasil 9 since 2018

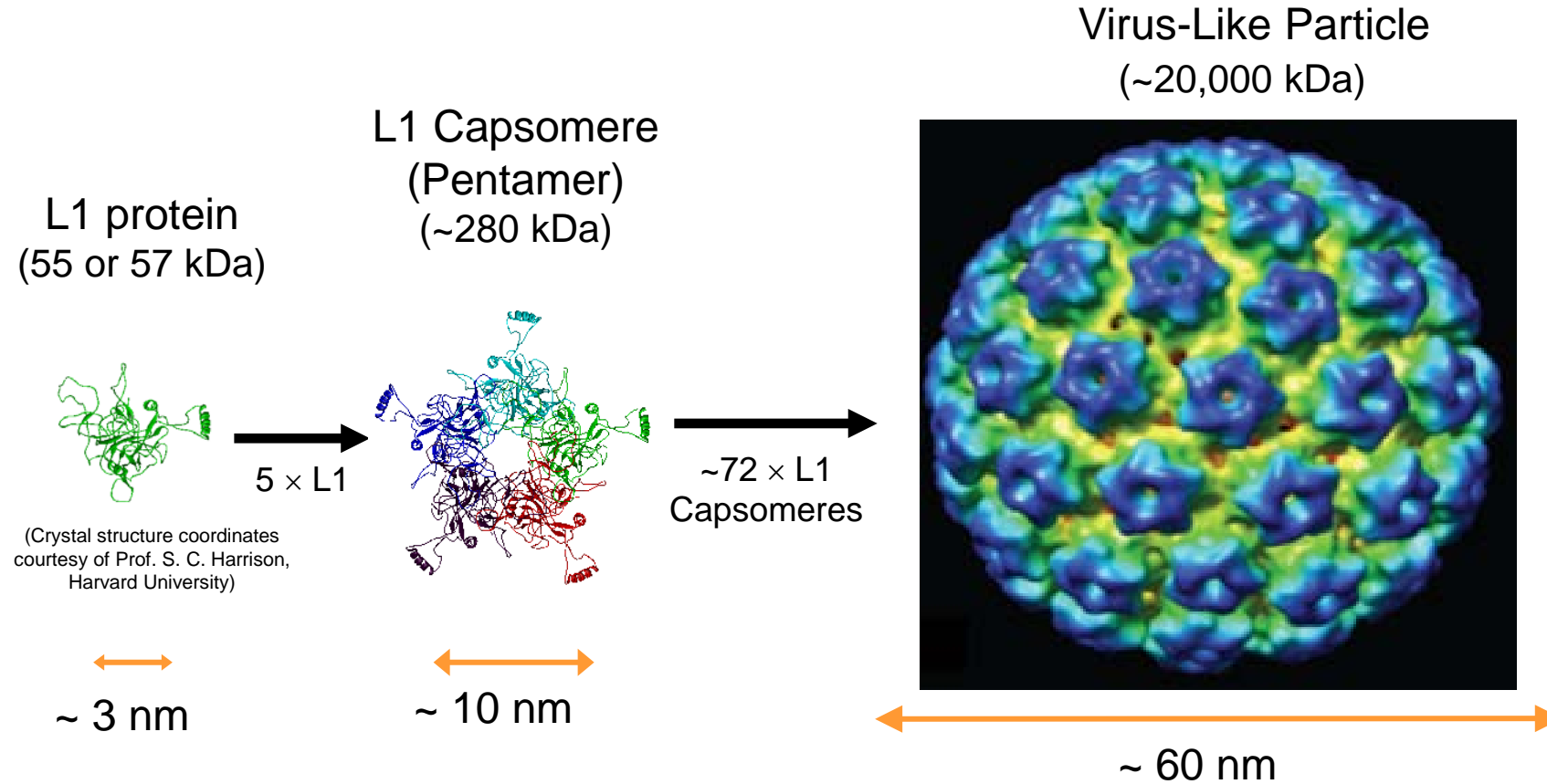




# CMC Aspects



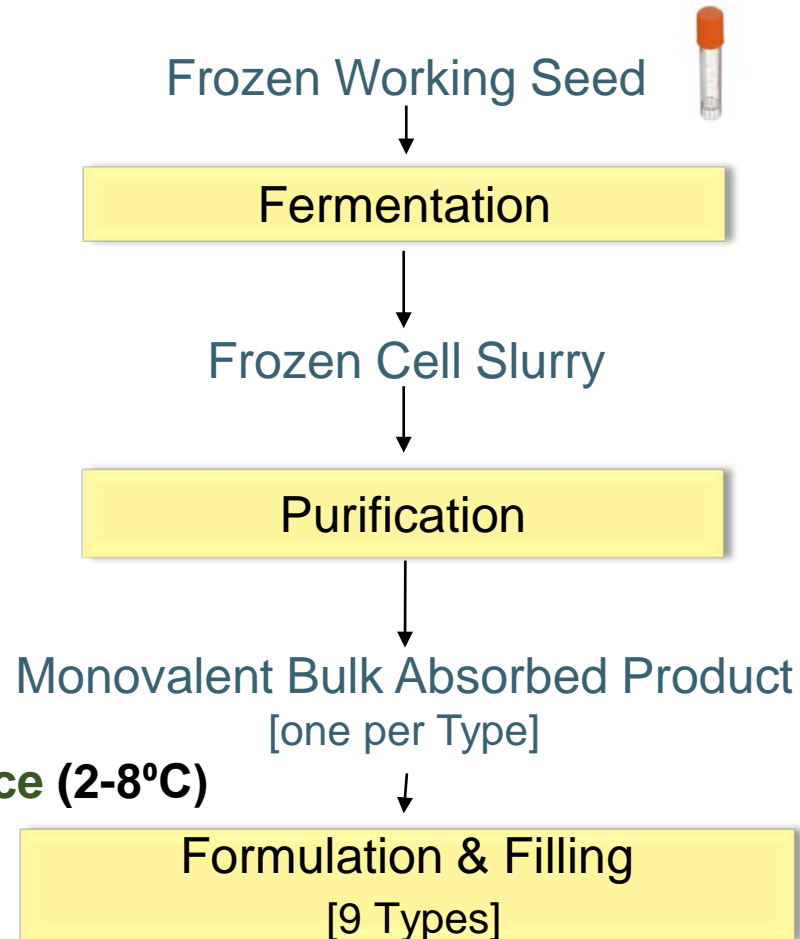
# GARDASIL<sup>®</sup>9 Based on Human Papillomavirus (HPV) Virus-Like Particle (VLP)



- Vaccine based on HPV major capsid protein, L1, self-assembled into virus-like particles (VLPs)
- Complex structure, but well characterized



# Gardasil<sup>®</sup>9 Manufacturing Process



## Opportunity:

- GARDASIL<sup>®</sup>9 developed based on Platform Process
- Monovalent Drug Substance: Ability to accommodate clinical development needs
- Optimization of the production, recovery and purification of the antigen for each type

## Challenges:

- Drug Product requires 9 distinct Drug Substance inputs
- Difference in scale of process for Drug Substance: Fermentation and Purification and Drug Product
- Inherent complexity of Manufacturing
  - Raw Material Variability
  - Type specific challenges
  - Yield variability

**Drug Product (2-8°C)**

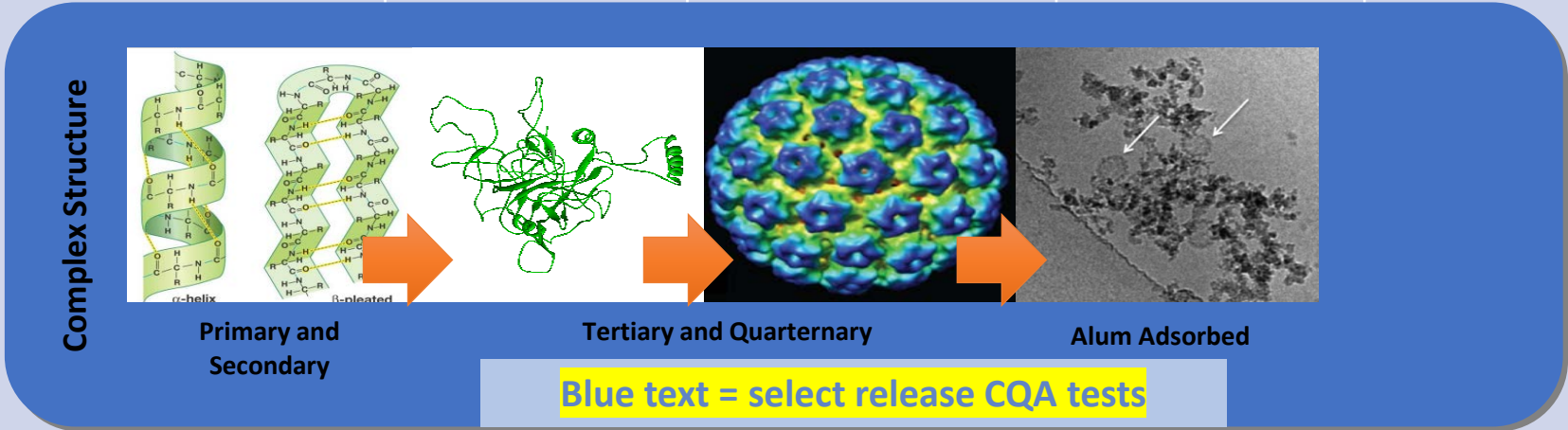
**Gardasil<sup>®</sup>9**



# GARDASIL<sup>®</sup>9 Amenable to Characterization: Robust Control Strategy Achievable

Physicochemical Properties	Biological Activity Identity	Purity	Impurities	Contaminants	Quantity
<u>Primary Structure</u> <ul style="list-style-type: none"> <li>• Peptide Map (Digestion, MALDI-MS)</li> <li>• Deamidation (Isoquant)</li> <li>• Denatured Free Thiols</li> </ul> <u>Secondary Structure</u> <ul style="list-style-type: none"> <li>• CD</li> <li>• FTIR</li> </ul> <u>Tertiary - Quarternary Structure</u> <ul style="list-style-type: none"> <li>• Native Free Thiols</li> <li>• Thermal Unfolding (DSC)</li> <li>• Morphology (TEM, CryoEM, AFM)</li> <li>• Monodispersity (TEM, SEC-HPLC)</li> <li>• Aggregation (DLS, Cloud Point, SPR)</li> </ul> <u>Other (DP)</u> <ul style="list-style-type: none"> <li>• <b>Aluminum</b></li> <li>• <b>PS-80</b></li> <li>• <b>pH</b></li> <li>• <b>Completeness of adsorption</b></li> </ul>	<u>Antigenicity (DS/DP)</u> <ul style="list-style-type: none"> <li>• <b>In Vitro Relative Potency (sandwich ELISA)</b></li> <li>• Solution Antigenicity (competitive ELISA – IC50)</li> <li>• Epitope Mapping (SPR)</li> <li>• Epitope-specific antigenicity (SPR)</li> <li>• <i>In Vivo</i> Potency (mouse ED50)</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Purity (SDS-PAGE) (DS)</b></li> </ul>	<u>Host-Cell</u> <ul style="list-style-type: none"> <li>• Protein (Western Blot)</li> <li>• Nucleic acids</li> </ul> <u>Product-Related</u> <ul style="list-style-type: none"> <li>• <b>Resistance to Proteolysis (SDS-PAGE) (DS)</b></li> </ul> <u>Process-Related</u> <ul style="list-style-type: none"> <li>• Protease</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Sterility</b></li> <li>• <b>Endotoxin</b></li> </ul>	<ul style="list-style-type: none"> <li>• <b>Protein concentration (DS)</b></li> </ul>

Release and Stability Indicating



[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_Scientific\\_Discussion/human/000703/WC500021140.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000703/WC500021140.pdf)

Zhao, et al (2013) Cell Press 31(11): 654-663; <http://www.tandfonline.com/doi/pdf/10.4161/hv.27316>

# Potency Assay and Implementation

## In Vitro Relative Potency Assay

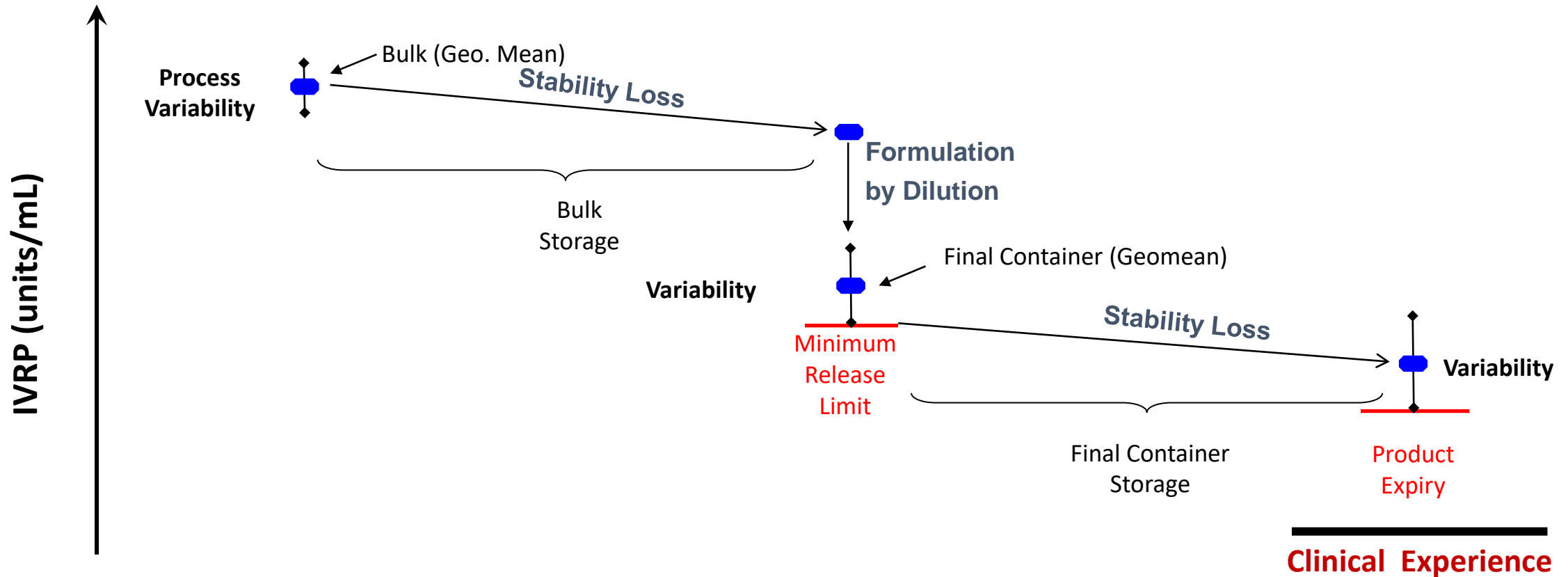
- ELISA technology
- Correlates with human immunogenicity and mouse potency
- IVRP measures specific antigenicity and is used for product release

## Implementation

- Relative potency format
- Reference lot = clinical lot
- Potency of first reference lot defined as its nominal protein dose values, and expressed in Units/ml
- Future reference lots calibrated against frozen standards

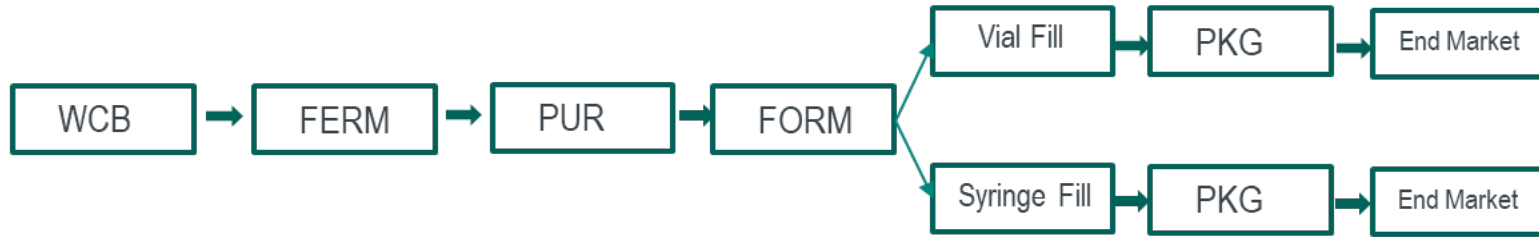
# Initial Release and Stability Specification

- Clinical performance known for pivotal lots
- Process/analytical capability used to set final specs
- Assurance that commercial lots not less potent
- Issue: Limited number of final container lots and Limited stability data
- Solution: Propagation of error model

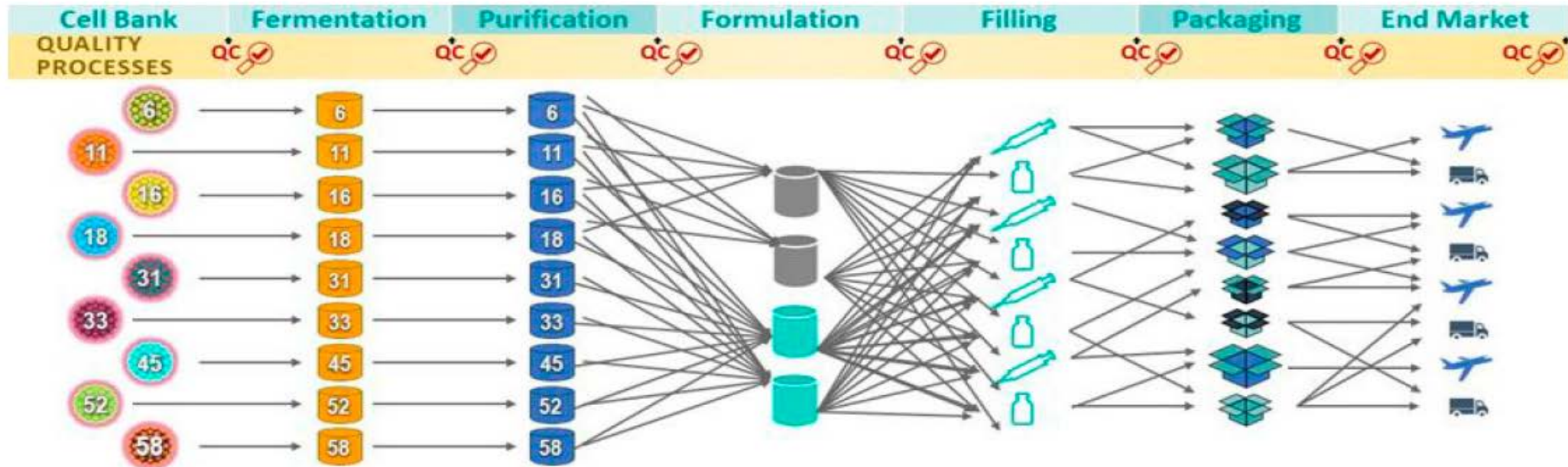


# Manufacturing Complexity: Supply Chain

Monovalent



“Simple” supply chain with a monovalent product that is filled into 2 finished good images: vials and syringes



QC=quality control – extensive quality control testing is required throughout the process and may vary by market.

# Summary

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The successful expansion of Gardasil<sup>®</sup> HPV type coverage to Gardasil<sup>®</sup>9 leveraged:

- A platform manufacturing process that enables manufacturing of multiple serotype with the same equipment train
- An integrated control strategy that relies on process and analytical control to ensure consistency and quality
- A flexible supply chain to meet changing demand
- A life cycle management approach to respond reactively and proactively to changes





# Acknowledgement

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Thomas Potgieter





# Seasonal Influenza overview and challenges

**BEVERLY TAYLOR**

**14 April 2021**

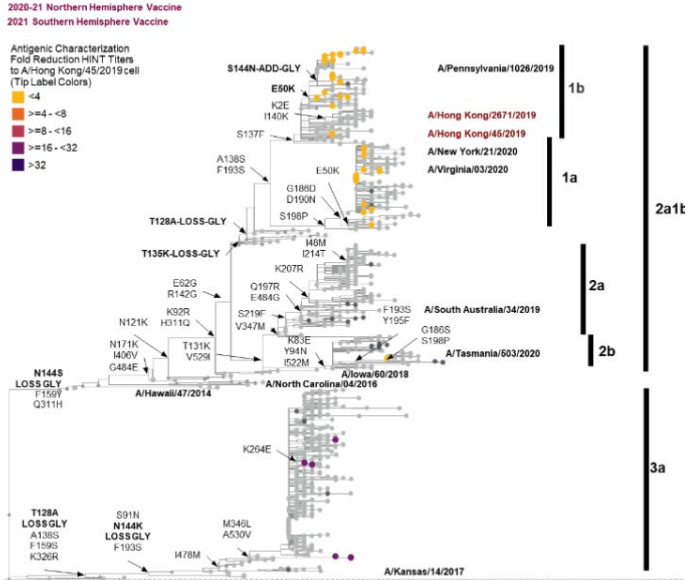
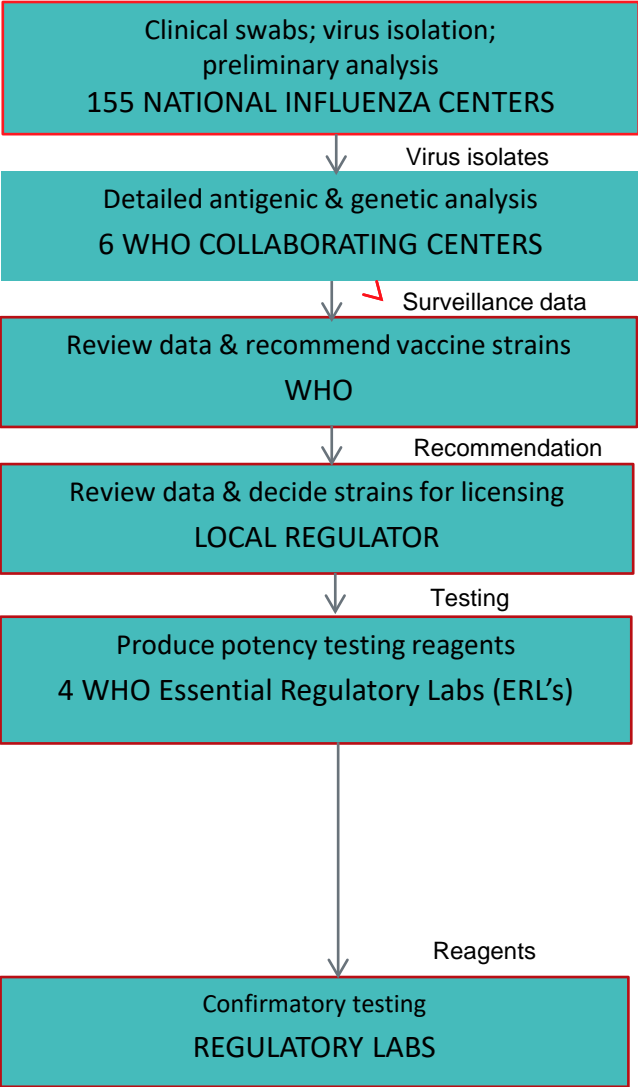
# Introduction

- To remain effective, the composition of seasonal influenza vaccines must be reviewed and updated for each season to include the HA antigens expressed by the most current circulating influenza wild-type viruses.
- The process to achieve this is lengthy and complex and requires extensive and ongoing collaboration between all stakeholders including influenza manufacturers, WHO, vaccine regulators, and global public health laboratories.
- The process begins with a review of recent global surveillance data the outputs which is used to inform the vaccine virus recommendations made by WHO.
- The vaccine virus recommendations which are provided in February for the Northern Hemisphere (NH) and in September for the Southern Hemisphere (SH) seasons, provide a guide to national public health authorities and vaccine manufacturers for the development and production of multivalent influenza vaccines for the upcoming influenza season.
- It is the responsibility of each national regulatory authority to approve the composition and formulation of the vaccines used in that country.

# Seasonal Influenza Overview and Challenges

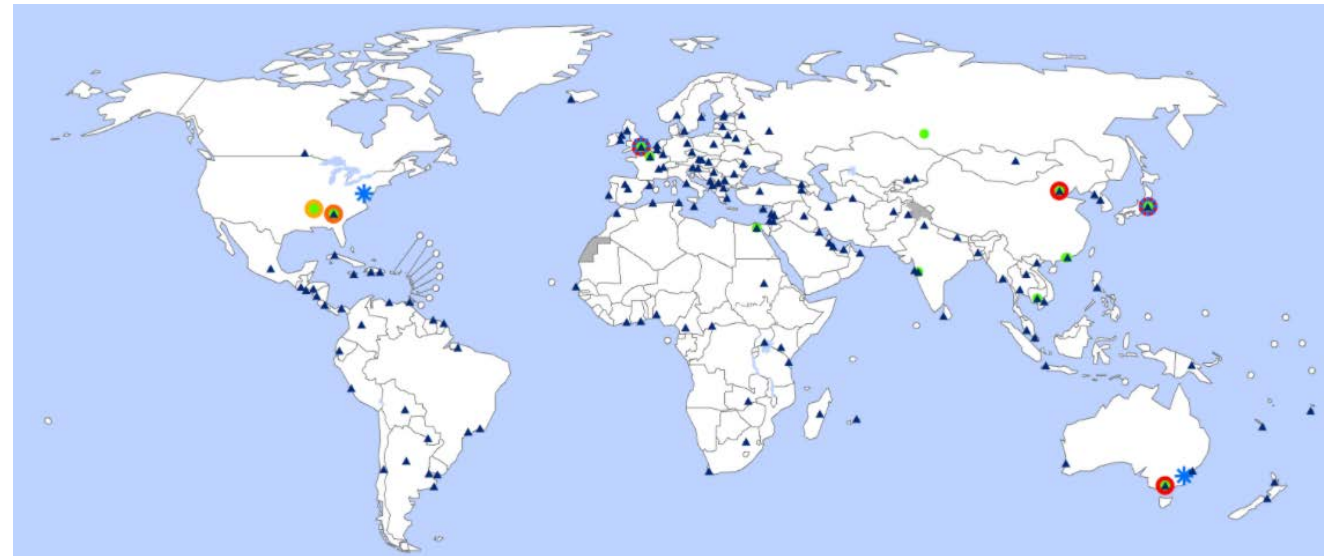
- Overview of WHO Global Influenza Surveillance and Response System (GISRS)
- Ongoing surveillance and tracking of seasonal candidate vaccine viruses (CVVs)
- Nagoya Protocol/National access and benefit sharing (ABS) legislation
- Timelines for seasonal influenza manufacturing
- Annual regulatory submissions to update product licenses
- Summary of challenges

# Overview of WHO Global Influenza Surveillance and Response System (GISRS)



# National Influenza Centres (NICs)

- NICs are national institutions designated by national Ministries of Health and recognized by WHO
- WHO co-ordinates a surveillance network of 155 laboratories in 125 countries
- Collect virus specimens in their country and perform preliminary analysis to identify and track changing strains as they circulate
- Ship representative clinical specimens and isolated viruses to WHO CCs for further analysis.



Data Source: Global Influenza Surveillance and Response System (GISRS), WHO  
Map Production: Global Influenza Programme  
World Health Organization



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# WHO Collaborating Centres (CC's)

- The NIC's forward representative influenza samples to one of six WHO CC's who carry out advanced antigenic and genetic analysis
- St. Jude's Hospital concentrates on influenza viruses with pandemic potential
- The CC's collate surveillance information twice per year for WHO strain recommendation
- Provide candidate vaccine viruses (CVVs) to reassortant labs and manufacturers
- Screen viruses for anti-viral resistance



Crick Institute, London



VIDRL, Melbourne



CDC, Atlanta



NIID, Tokyo



CNIC, Beijing



St Jude's Hospital, Memphis

# Essential Regulatory Laboratories (ERL's)



**NIBSC labs in South Mimms**

Photo courtesy of NIBSC

There are four Essential Regulatory Laboratories (ERLs) within GISRS who are responsible for potency assay reagent preparation and calibration:

- NIBSC, UK
- CBER, US
- NIID, Japan
- TGA, Australia



# Generation of Virus Seeds by Reassortant Labs

- Reassortant labs prepare high yield reassortant viruses for inactivated influenza vaccine manufacturing.
- There are 6 reassortant laboratories:
  - New York Medical College (NYMC), US
  - NIBSC, UK
  - Seqirus, Australia
  - CBER, US
  - CNIC, China
  - Sanofi, US
- High yield reassortant viruses are made available to all manufacturers

**Note: Reassortant labs are not part of the GISRS but interact closely with it.**



## Ongoing Surveillance Monitoring and tracking of available CVVs

- Regular reviews of surveillance websites such as WHO Fluupdate, CDC Fluview, ECDC Flu news etc.
- Surveillance updates provided at bi-annual NIBSC meetings (Jan and July) and BIO/FDA meeting (Dec) as well as through summaries of internal WHO TCs leading up to strain recommendation
- Tracking surveillance and availability of CVVs for manufacturing through bi-weekly, WHO chaired Technical TCs and real-time spreadsheet of viruses of interest, stage of preparation of CVV's and availability to manufacturers.
- Year round activity as strain recommendations are changed twice each year (northern hemisphere and southern hemisphere seasons)

# Development of CVVs representative of circulating strains

- Receive CVVs of interest to develop high growth reassortant viruses or temperature sensitive viruses to be used in manufacturing.
- Aim is to cover as many of the circulating virus clades and sub-clades as possible prior to strain recommendation
- The phylogenetic trees of the viruses becoming more and more complex as they are now based on genetic sequences providing much more detail on differences between viruses
- Difficult to determine which genetic sequence differences result in antigenic changes
  - Not clear a strain change is required
  - Not clear which viruses are antigenically similar (“like-strains”)
- Manufacturers evaluation of CVVs for suitability in manufacturing process and yield
- Production of Master and Working Seeds

# Nagoya Protocol\*/ABS Legislation

- An increasing number of countries have Nagoya Protocol (NP) or National Access and Benefit (ABS) Legislation in place
- **Inclusion** of pathogens, including influenza, under national ABS legislation **is already causing delays and disruptions.**
- ABS legislation continues to impact sharing of influenza Genetic Resources (GRs) and, has been/is being amended in a number of countries to include DSI/GSD
- **Bilateral negotiation** of access and benefit-sharing contracts, including prior informed consent (PIC) and mutually agreed terms (MAT), are lengthy and **block any possibility of quickly responding to public health emergencies.**
- **Pathogens know no borders**, global alignment on ABS is essential for responses to global health threats.
- **Legal certainty** regarding the status of pathogen sharing under ABS legislation is **essential.**

\*Convention on Biological Diversity (Montreal, CAN) signed 29Oct'10, came in to force 12Oct'14, describes Access & Benefit Sharing (ABS) of GRs and traditional knowledge that is accessed for potential research/use and ensures that users and providers agree on fair and equitable sharing of benefits arising from their use

DSI, Digital Sequence Information; GSD, Genetic Sequence Data



## Current Situation

- Influenza vaccine virus recommendations are dynamic, with several candidate vaccine viruses (CVVs) being considered for each season
- Most NICs continue to supply influenza viruses under the agreed Terms of Reference as part of GISRS, however there is a lack of legal clarity if the viruses can be used for vaccine manufacturing and research
- It is neither feasible nor efficient to start bilateral negotiations with all CVV provider countries prior to confirmation of recommended viruses. Once the vaccine recommendation is made, there is very little time for manufacturers to conclude bilateral negotiations in time for manufacturing campaign
- NP and ABS legislation differs in each country, is often only available in the local language which poses challenges with interpretation of requirements
- It is not always clear which viruses may be considered as “like” viruses to the recommended virus and could be used as an alternative in manufacturing.
- Several cases of delays in influenza virus sharing due to implementation of the NP/ABS legislation have been already been experienced.

# Examples of Impact of Nagoya Protocol/ National ABS Legislation

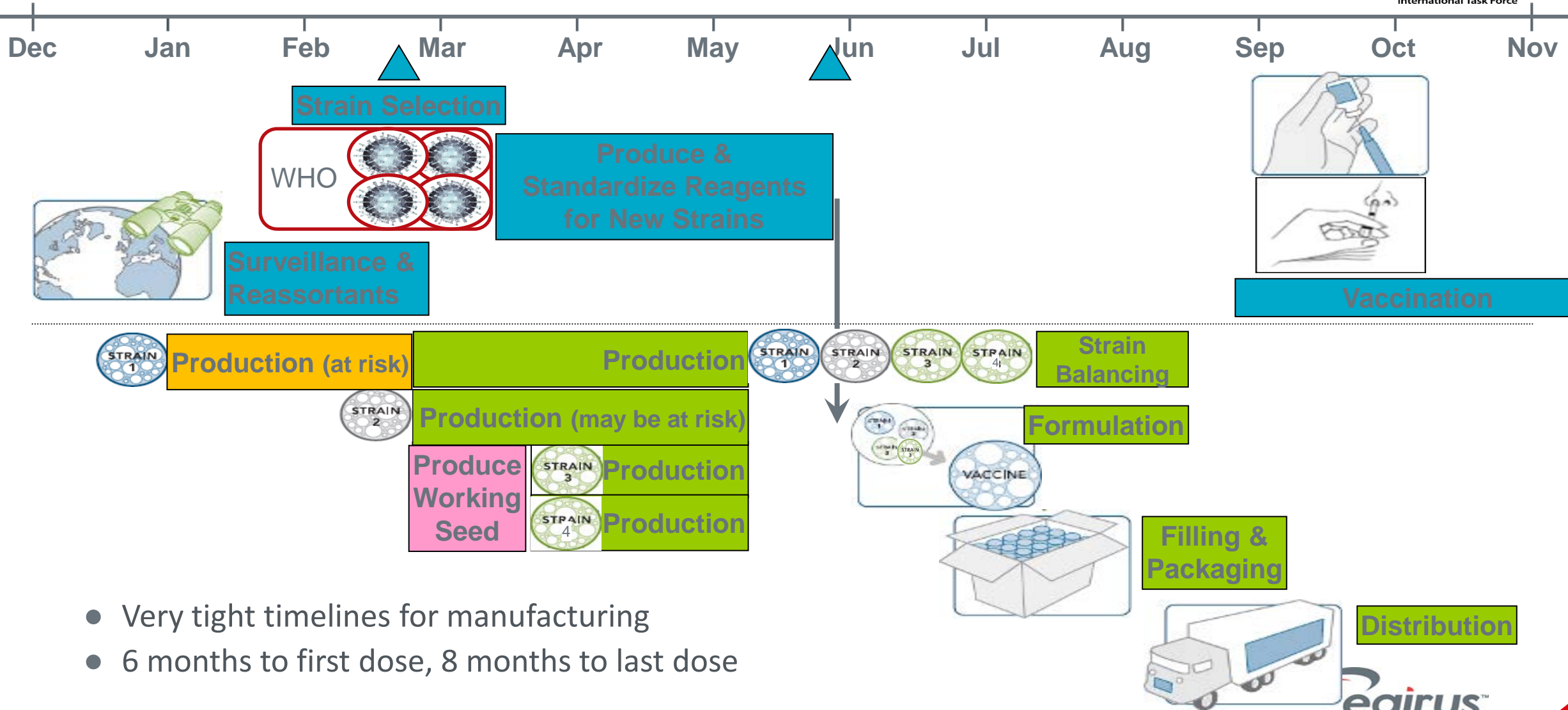
Since September 2018, over 30 influenza viruses which had been shared with WHO CCs have been impacted by national NP/ABS legislation incurring delays from 3 weeks and up to 5 months before legal clarity has been obtained. In several cases this has resulted in the viruses being available too late for the upcoming influenza season. For some of the more recent viruses legal clarity is still outstanding.

- On 26 Feb 2021, WHO selected a H3N2 influenza strain from Cambodia as a reference strains for use in the NH 2021/22 influenza season. Manufacturers checks indicated that Cambodia had not yet enacted ABS legislation and assumed that use of the Cambodia strain was not being impeded by any potential ABS obligations.
- Days later manufacturers discovered that WHO had contacted Cambodia for clarification and had only received permission for the virus to be used for “non-commercial purposes”. WHO then held discussions with Cambodia to ensure that “commercial use” of the virus was possible and to try to have the benefits accrued by Cambodia through being part of GISRS recognised and accepted.
- This impacted
  - Timing of decisions on which virus to use by manufactures
  - Whether critical reagents would be prepared and made available to manufacturers
  - Possibility that the virus could not be used even though it had been listed on the WHO website for a month
  - Possibility of manufactured batches being discarded
- “Commercial use” approved but written confirmation that no monetary benefits still outstanding

# Seasonal Influenza Vaccine Manufacturing Timeline for NH Supply



Influenza Vaccine Supply International Task Force



- Very tight timelines for manufacturing
- 6 months to first dose, 8 months to last dose



# Annual Updates to Product Licenses

- Licensed influenza vaccine manufacturers must submit a supplement to their product license for review for each season and obtain regulatory approval before the updated version of the influenza vaccine containing new virus antigens can be distributed.
- The supplements for live attenuated, inactivated and recombinant protein seasonal influenza vaccines do not require additional clinical data specific for the new strain prior to approval of the new strain to verify adequate attenuation.
- Supplements vary by region/country and include:
  - Virus Manufacturing Seed - derivation and seed lot release certificate
  - Potency reagents – reagent qualification and potency assay validation
  - Drug substance – process qualification (e.g. inactivation kinetics), monobulk release and stability data
  - Drug product – multivalent product release and stability data
- Workload increases with the number of strain changes



# Vaccine Mismatch

- For some influenza seasons the antigenic drift of the viruses, particularly H3N2s results in a mismatch between the circulating strains and the strains included in the vaccine (e.g. NH 2014/2015 season when a new H3N2 emerged quickly after the strain recommendation)
- Several years ago discussions facilitated by HHS BARDA looked at how this could be addressed including delayed strain recommendation and development of new manufacturing platform technologies
- Recognised that new technologies could allow faster response in manufacturing, but also need to consider time taken for product characterisation, updating licenses, approvals from regulatory agencies and product testing and release.
- Challenges:
  - Need to consider impact of later strain recommendation on vaccination campaigns in all countries/regions
  - Extremely challenging to change a strain in a multivalent vaccine mid-campaign-potential for product write-offs
  - See different predominant viruses in different regions for some seasons
  - Preference for one vaccine per season with possibility for additional monovalent boost based on severity/risk
  - Concern that delays could impact preparations for the following season
  - Public information campaigns would be required to support later vaccine availability to avoid decrease in vaccination rates

## Summary of Seasonal Influenza Challenges

- Requires year round surveillance monitoring
- Increasing complexity of virus clades and sub-clades results in more CVVs to consider
- NP/ABS legislation is increasingly a barrier to the access and use of CVVs
- Manufacturing timelines are extremely tight and any delays will impact vaccine supply
- Annual update of licenses is labour and time intensive
- Risk of vaccine mismatch due to ever evolving viruses
- Not even touched on influenza viruses with pandemic potential

Always on the front line and never a dull moment!

# Thank You!



# Placeholder: Clinical introduction

# Placeholder: Immunological perspectives



# Lessons learned in the development of multivalent bi-component Norovirus vaccine

COVAX Workshop 14 April 2021

Jim Sherwood, Scientific Director, Norovirus Vaccine Program  
Takeda Global Vaccine Business Unit



Better Health, Brighter Future

# Disclaimers

The information contained in this presentation is intended for use at this COVAX Workshop only.

TAK-214 has not been approved for use in indications under investigation in some of the trials or studies discussed herein and there is no guarantee it will be approved for such use.

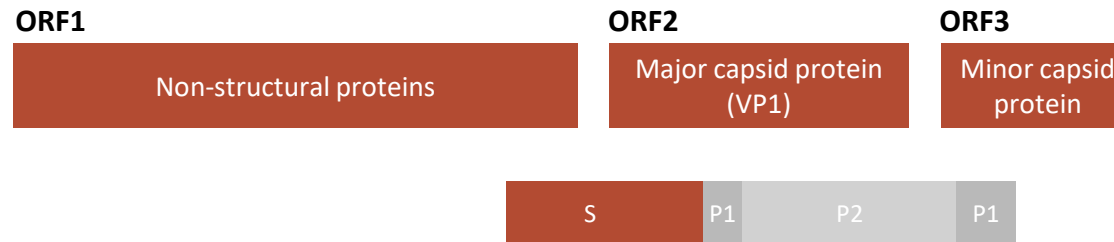
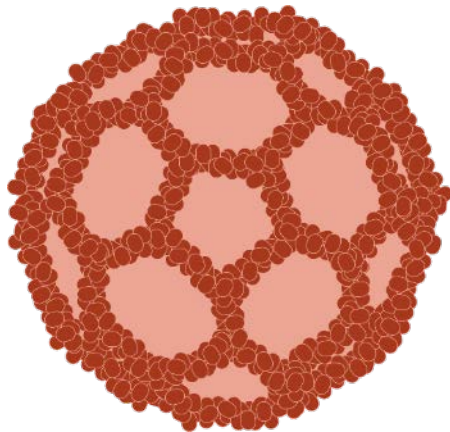


# Overview

- What is norovirus
- Disease and epidemiology
- Takeda's norovirus vaccine candidate, TAK-214
- Lesson 1: genetic diversity and choice of antigens  
cross-reactivity/protection  
competition / interference between antigens
- Lesson 2: assessment of immunogenicity, assay development  
immunobridging
- Lesson 3: selection of endpoints in efficacy trials

# Norovirus structural characteristics

- Noroviruses are small, non-enveloped, icosahedral viruses<sup>1</sup>, in the family *Caliciviridae*<sup>2</sup>
- 180 molecules of the norovirus capsid protein (VP1) are arranged as dimers, each divided into<sup>1,3</sup>:
  - Shell (S) domain: Remains relatively conserved
  - Surface-exposed protruding (P) domain: Variability results in strain designation



ORF, open reading frame

1. Atmar RL, et al. Food Environ Virol 2010; 2. Glass RI. NEJM 2009; 3. Prasad BV, et al. Science 1999

# Norovirus genotypes – 2015 vs 2019

Based on capsid sequences alone:

- 7 genogroups (2 infecting humans)
- 39 genotypes<sup>1</sup>

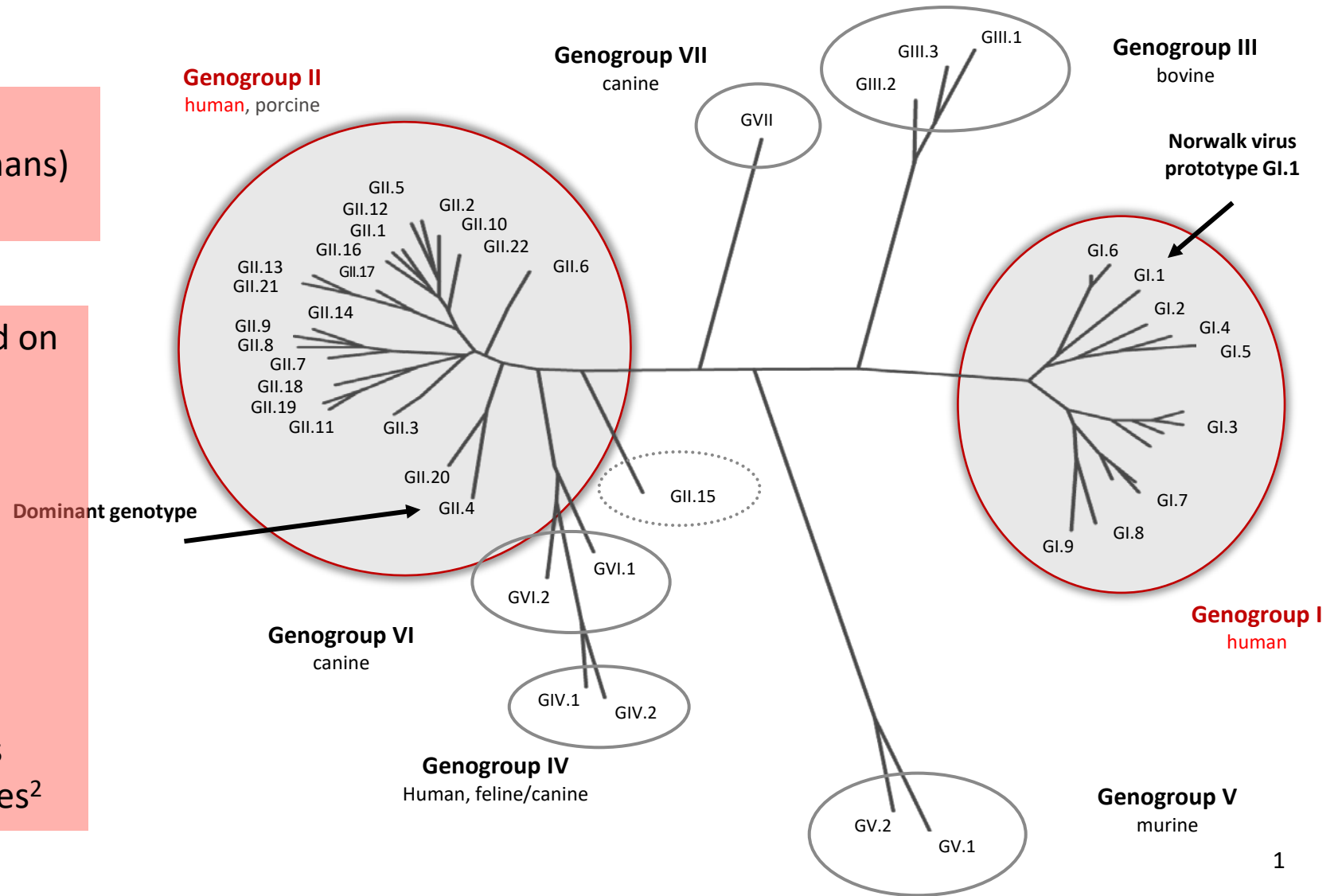
Update classification system based on capsid as well as polymerase sequences.

For capsid sequences:

- 10 genogroups + 2 tentative genogroups
- 49 genotypes + 5 tentative genotypes

For polymerase sequences:

- 8 P-groups + 2 tentative groups
- 60 P-types + 16 tentative P-types<sup>2</sup>



1. Vinje, J Clin Micro 2015 2. Chhabra, J Gen Virol 2019

A light gray world map is centered in the background of the slide. The map shows the outlines of continents and countries. Overlaid on the map is text in a bold, dark red font.

**Norovirus is highly infectious and responsible for widespread human disease<sup>1</sup>:**

**Globally:  
699 million cases  
and 200,000 deaths  
annually<sup>2</sup>**

1. Patel MM, et al. J Clin Virol 2009; 2. Bartsch SM, et al. PLoS One 2016

# Lesson 1 – selection of antigens and formulation

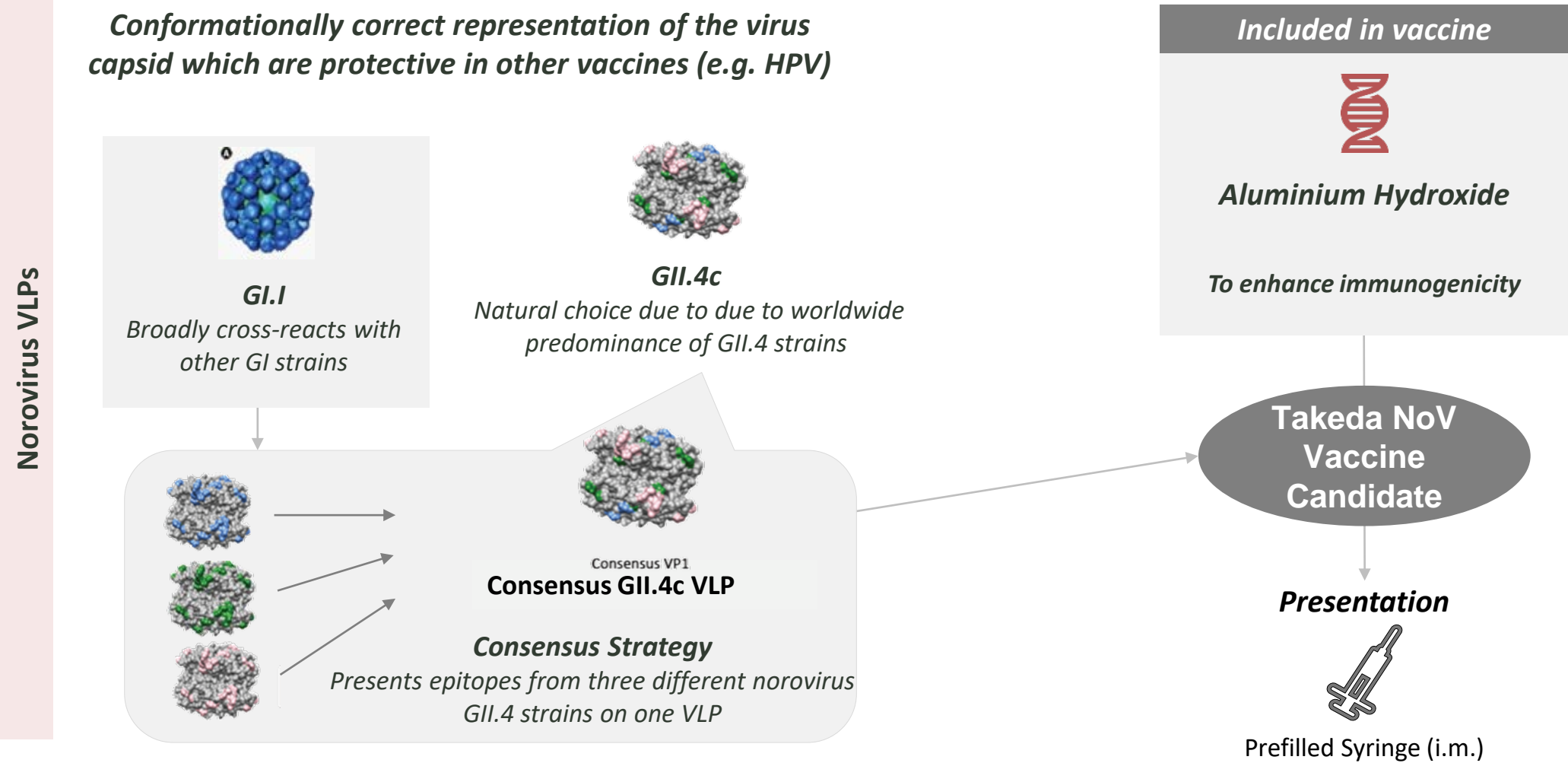
## Factors considered in developing TAK-214

- Epidemiology
  - Include representative genotypes from the two genogroups that infect humans (at the time the vaccine was designed)
  - Strain variation
  - Incidence of different genotypes/strains by age group
- Cross reactivity (serological)- may or may not indicate cross protection
- Possible interference / competition of antigens (only considered later in the program)
- Selection of dose and regimen; may be different for other age groups (older adults, children)

# Takeda's Bivalent Norovirus vaccine candidate: TAK-214

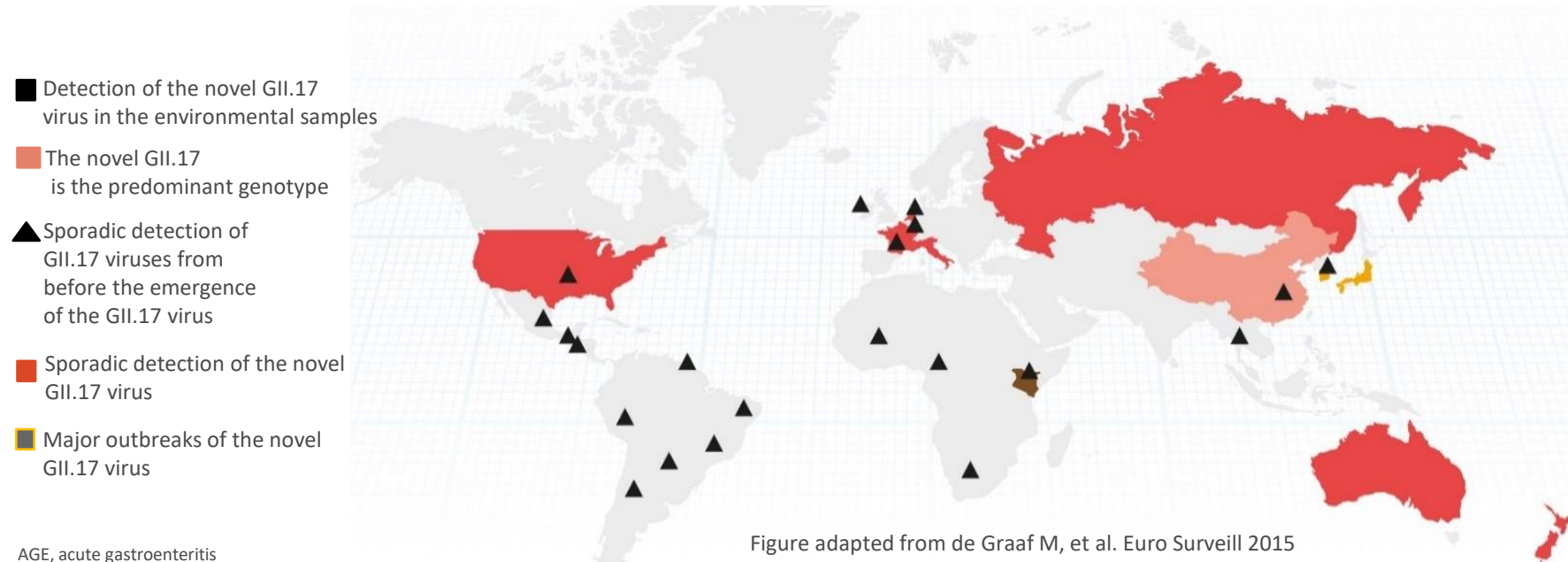
## Virus-Like Particles Antigens (VLPs)

## Adjuvant



# Emergent strains; importance of surveillance over time

- Noroviruses undergo genetic evolution through both antigenic drift and shift, and new genotypes and subtypes emerge approximately every 3 years<sup>1</sup>
- GII.4 is the dominant genotype globally<sup>2</sup> and caused all major norovirus epidemics in the last decade<sup>3</sup>
- Emergent GII.4 strains rapidly replace existing strains and can cause seasons with unusually high norovirus activity<sup>4-9</sup>
- A novel GII.17 variant was the dominant norovirus strain in Asia in 2014–2015, and was associated with an increase in AGE outbreaks<sup>10</sup>. This variant was present in the US at the beginning of the 2014–2015 season, suggesting that GII.17 may have the potential to become a new strain of global importance<sup>11</sup>



1. White PA, et al. Clin Microbiol Infect. 2014; 2. Hoa Tran TN, et al. J Clin Virol 2013; 3. Bull RA, et al. PLoS Pathog 2010; 4. CDC MMWR 2011; 5. Holzkecht BJ, et al. PLoS One 2015; 6. Debbink K, et al. J Infect Dis 2013; 7. Motomura K, et al. J Virol 2008; 8 Okada M, et al. Arch Virol 2007; 9. Sakon N, et al. Jpn J Infect Dis 2007; 10. de Graaf M, et al. Euro Surveill 2015; 11. Parra GI, et al. Emerg Infect Dis 2015

# Optimization of antigen formulations – NOR-107

A safety and immunogenicity study of various vaccine formulations in healthy adults

- Modified factorial design
- Compared different combinations of antigen, MPL, Alum and 1 vs 2 doses in two age groups

## Results

- An imbalanced formulation with GII.4 > GI.1 provided the best response for GII.4
- In primed healthy adults, neither MPL nor a second dose conferred any additional immunological benefit that we were able to measure (Ab titres, persistence, CMI)

## Caveat

- All subjects had been exposed to norovirus prior to entry

Leroux-Roles, J Infect Dis, 2018

Total Subjects, N=420

11 Formulation Arms      Stratified by Age (years)/ Dose Group

Arm	Formulation (µg GI.1/GII.4/MPL*)	Total N	Stratified by Age (years)/ Dose Group			
			17 to 49/ One Dose (N)	50 to 64/ One Dose (N)	17 to 49/ Two Doses (N)	50 to 64/ Two Doses (N)
1	15/15/50	30	15	15	-	-
2	15/50/50	30	15	15	-	-
3	50/50/50	30	15	15	-	-
4	15/15/15	30	15	15	-	-
5	15/50/15	30	15	15	-	-
6	50/50/15	30	15	15	-	-
7	15/15/0	30	15	15	-	-
8	15/50/0	60	15	15	15	15
9	50/50/0	30	15	15	-	-
10	50/150/0	60	15	15	15	15
11	15/50/0 (167 µg Aluminum)	60	15	15	15	15

\*Aluminum content is 500 µg unless otherwise stated.  
Red formulation arms are randomized into 1 and 2 dose groups.  
MPL=Monophosphoryl lipid A



## Lesson 2 – assessment of immunogenicity – choice of assays

- Until 2019 norovirus were non-cultivable and a neutralization assay using this system is still under development<sup>1</sup>
- A correlate of protection has been proposed but has yet to be confirmed<sup>2</sup>
- Early trials explored binding Immunoglobins (serum IgG, IgA and a pan-Ig assay and salivary IgA)<sup>2,3</sup>
- Noroviruses bind to human cells through attachment with histo-blood group antigens (HBGA) and a blocking assay for this binding has been developed<sup>2</sup>
- Takeda is currently in the process of validating an HBGA blocking assay for use in late phase 2 and phase 3 development even though this is not a direct measurement of neutralization

1. Estes, Viruses 2019 2. Atmar, Clin and Vacc Immuno 2015 3. Bernstein J Infect Dis 2014

## Lesson 3 – selection of endpoints in efficacy trials

- Adult norovirus disease is outbreak driven – there are challenges in selecting the right population as well as the right efficacy endpoint.
- With outbreak driven disease there will always be an element of chance
- We used a “standard approach” to assess efficacy against vaccines components
- We considered other options:
  - “all noro” as primary endpoint
  - Co- primary endpoints
- Co infections? We chose to exclude endpoints with a co-pathogen in the protocol
- What about cross-protection? We included efficacy against non-vaccine genotypes as an exploratory endpoint.
  
- The NOR-211 story

# NOR-211 Trial Design

- This was a double-blind, randomized, placebo-controlled study (**NCT 02669121**) to assess the efficacy of TAK-214 against norovirus associated acute gastroenteritis (AGE) in adults.
  - Primary objective was vaccine efficacy against moderate to severe norovirus AGE due to genotypes contained in the vaccine (GI.1/GII.4)
  - Secondary objective was vaccine efficacy against moderate to severe norovirus AGE due to any genotype
- The design was case driven with 30 primary endpoints required to provide 80% statistical power to reject the null hypothesis; primary objective would be considered met if the lower bound of the 95% CI was >0.
- Performed over two (winter) seasons: 2016-17 and 2017-18.
  - Location was US Navy Recruit Training Command, Great Lakes, IL, USA.
  - Participants were 18–49 year-old recruits randomized to two groups to receive:
    - one intramuscular dose of TAK-214 (n = 2,355) or saline placebo (n = 2,357)

## NOR-211 Efficacy outcomes – Norovirus AGE cases

	Placebo (N=2377)	TAK-214 (N= 2371)
<b>Identified Norovirus genotypes (all AGE severities)</b>		
GI.1	0	1
G1.7a	0	1
<b>GII.2</b>	<b>24</b>	<b>15</b>
GII.4	5	2
<b>AGE severity</b>		
Did not meet mild definition	0	1
Mild	2	6
Moderate	10	4
Severe	17	8
<b>Cases meeting Primary endpoint definition</b>		
Vaccine norovirus strains	5	1
<b>Cases meeting Secondary endpoint definition</b>		
All norovirus strains	26	10

No cases of co-infection with *Salmonella*, *Shigella* or *Campylobacter* occurred.

# NOR-211 Efficacy outcomes

- **Based on the observed epidemiology we amended the SAP to allocate alpha error and allow analysis of the secondary endpoints**
- **Primary endpoint** = prevention of moderate /severe AGE due to vaccine genotypes of norovirus was based on 5 cases in placebo arm, 1 in TAK-214 arm (all GII.4).
  - **Vaccine efficacy (VE) of 80.0% (99.99% CI, -1318.1 to 99.7; p = 0.142)**
  - **Lower bound of the 99.99% CI for VE was below 0% so primary objective was not met**
- **Secondary endpoint** = prevention of moderate/severe AGE due to any genotype of norovirus was based on 26 cases (21 GII.2 and 5 GII.4) in placebo arm, 10 (9 GII.2 and 1 GII.4) in TAK-214 arm.
  - **Vaccine efficacy (VE) of 61.8% (95.01% CI, 20.8 to 81.6; p = 0.0097)**
- **Ad hoc analysis** = prevention of moderate/severe AGE due to GII.2 genotype of norovirus was based on 30 cases, 21 in the placebo arm and 9 in the TAK-214 arm
  - **Vaccine efficacy (VE) of 57.4% (95% CI, 7.0 to 80.5; p=0.0321)**

Thank You



**Takeda Pharmaceutical Company Limited**



SANOFI PASTEUR 

14<sup>th</sup> April 2021

MAT-GLB-2101456/MAT-AU-2100830

## High dose influenza vaccine: trivalent to quadrivalent

Kevin Yin, Global Medical Product Lead

# Outline

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- **Emergence of influenza strains & vaccines valency**
- **Licensure of influenza vaccines & antibody response**
- **High dose (HD) influenza vaccine**
  - Registration of HD trivalent vaccine
  - Immunobridging approach to license HD quadrivalent vaccine





# Valency increase for influenza vaccines is not new

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- Influenza strains emerge over time → ↑ valency in vaccines

Circulating strains  
since 1938

1 → 4

Standard dose vaccines  
(unadjuvanted; for all ages)

Monovalent  
→ quadrivalent

IIV-HD vaccine  
(for 65+)

Trivalent from 2009

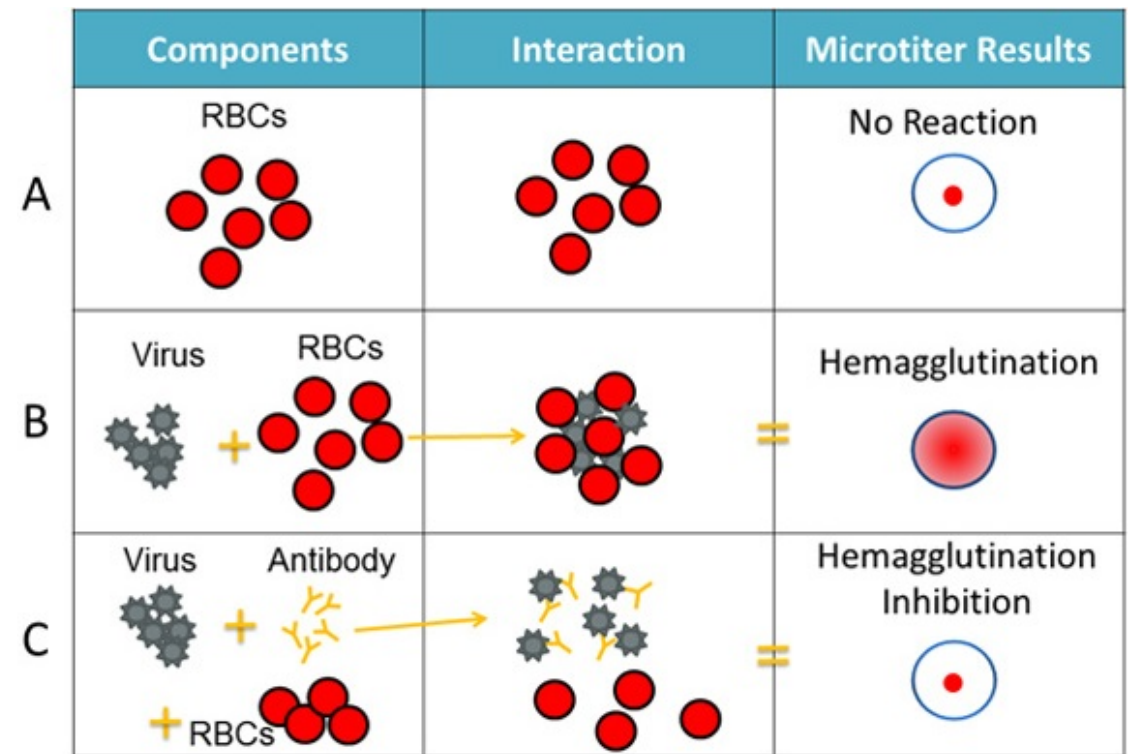


Quadrivalent from 2019

# Influenza vaccines: licensure based on antibody response

- Antibody level measured by haemagglutinin inhibition (HI) assay
- HI titre (e.g. seroconversion\*) = 'proxy' correlate of protection
- Efficacy trials important to confirm protection & necessary to claim superiority<sup>1</sup>

\* A predefined increase in serum antibody concentration or titre  
**Reference:** 1. European Medicines Agency (EMA). Guideline on Influenza Vaccines (Non-clinical and Clinical Module). 2016;  
[https://www.ema.europa.eu/en/documents/scientific-guideline/influenza-vaccines-non-clinical-clinical-module\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/influenza-vaccines-non-clinical-clinical-module_en.pdf)



# HD: a newer influenza vaccines for adults 65+

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- **4x the antigen of standard dose unadjuvanted vaccine (IIV3-SD)**
- **Licensure of IIV3-HD**

## Phase III trial (2006-07)<sup>1</sup>

- Superior antibody response over standard of care (IIV3-SD)



## Accelerated licensure by FDA (2009)

- Commitment to post-licensure efficacy study



## Post-licensure efficacy trial (2011-13)<sup>2</sup>

- Superior efficacy over standard of care (IIV3-SD)

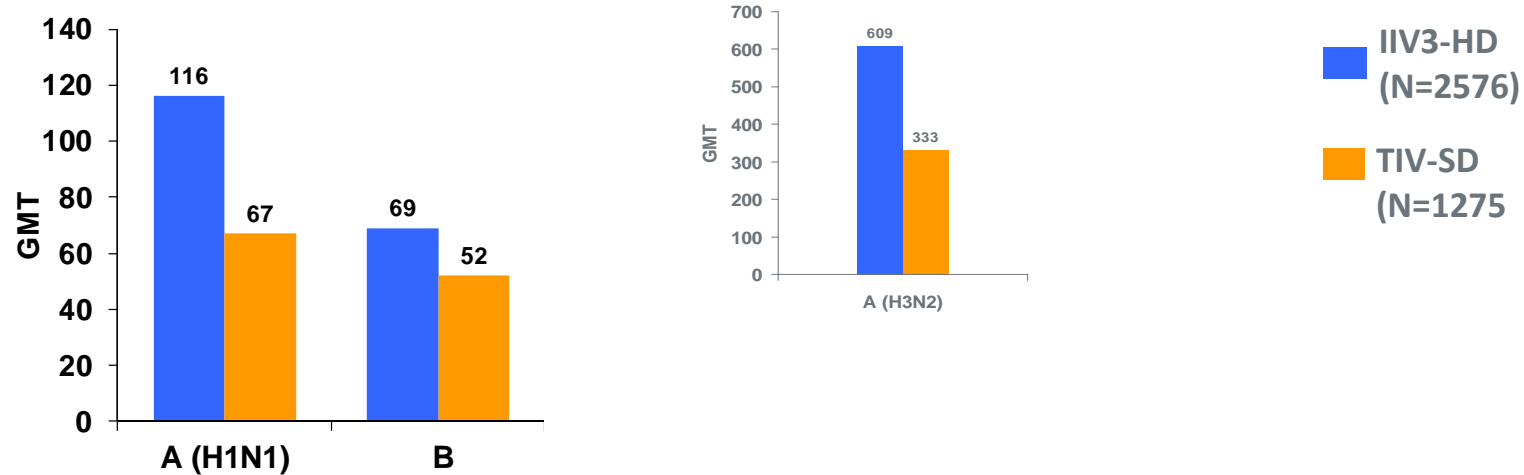
**References:** 1. Falsey et al. *J Infect Dis* 2009; 200: 172-180; 2. DiazGranados et al. *N Engl J Med* 2014; 371: 635-645

**Abbreviations:** IIV3-HD=high dose trivalent influenza vaccine; FDA=US Food and Drug Administration; IIV3-SD=standard dose, unadjuvanted trivalent influenza vaccine

# IIV3-HD: superior\* antibody response over IIV3-SD

---

- Phase III RCT with 3,851 Americans 65+ in 2006-07
- Superior antibody response for 2 of 3 strains



- Acceptable reactogenicity

\* Superiority was achieved if the lower bound of 95% confidence interval for the difference in seroconversion rates was >10%

Reference: Falsey et al. J Infect Dis 2009; 200: 172-180

Abbreviations: GMT=geometric mean titre; IIV3-HD=high dose trivalent influenza vaccine; RCT=randomised controlled trial; ; IIV3-SD=standard dose, unadjuvanted trivalent influenza vaccine

# IIV3-HD induced superior\* efficacy over IIV3-SD

---

- Phase IV RCT with 31,989 Americans 65+ in 2011-12 & 2012-13
- Results
  - Superior efficacy against lab-confirmed influenza: 24%
  - ↓ risk of serious events in IIV3-HD arm
  - No safety concern identified



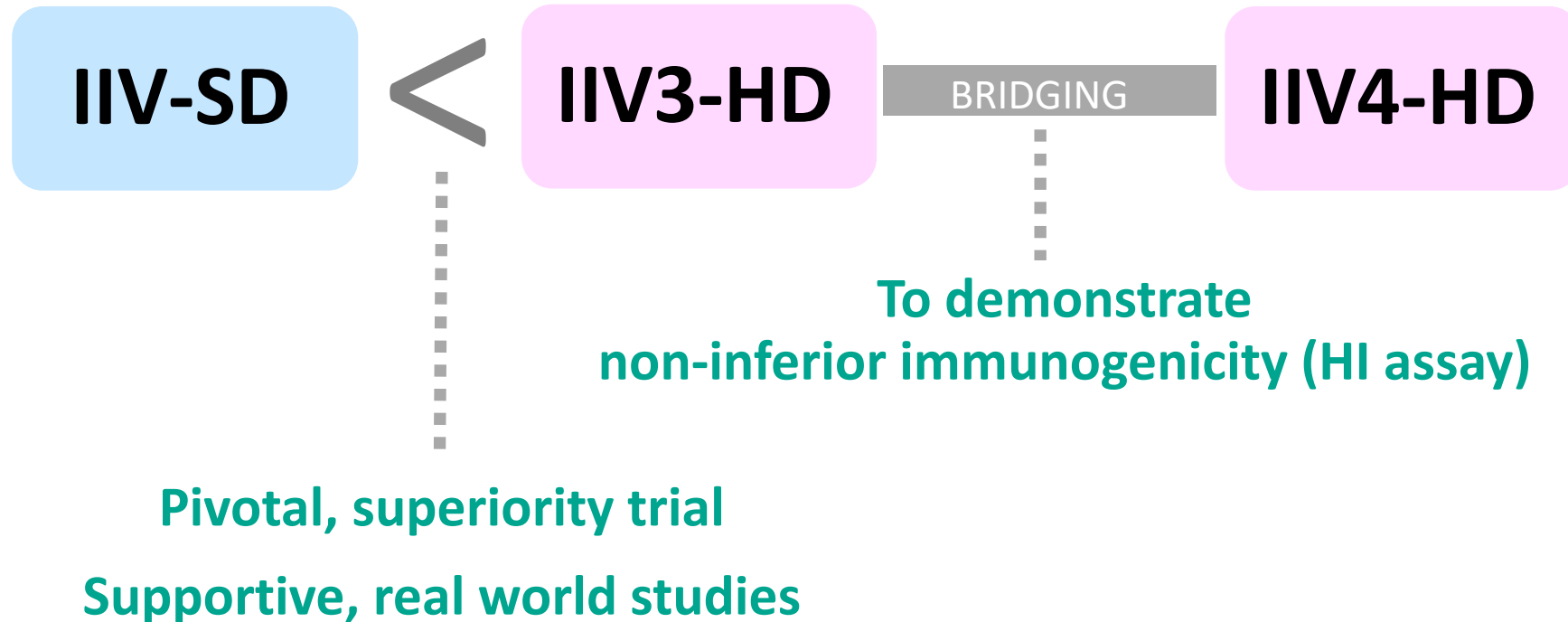
\* As agreed with FDA, superiority was achieved if the lower bound of 95% confidence interval exceeded 9.1%

**References:** DiazGranados et al. *N Engl J Med* 2014; 371: 635-645; DiazGranados et al. *Vaccine* 2015; 33: 4988-4993

**Abbreviations:** IIV3-HD=high dose trivalent influenza vaccine; RCT=randomised controlled trial; IIV3-SD=standard dose, unadjuvanted trivalent influenza vaccine

# IIV3-HD → IIV4-HD: immunobridging study

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- Based on demonstration of the non-inferior immunogenicity of IIV4-HD versus IIV3-HD, efficacy/effectiveness data of IIV3-HD to be inferred to IIV4-HD
- This approach recognised authorities; IIV4-HD now licensed in FDA, Europe & 4 other countries

# Immunobridging RCT of IIV4-HD



## Primary and Secondary Objectives

**1 Non-inferior Immunogenicity (HAI assay)**  
geometric mean titer ratios and seroconversion rates

**2 Superior Immunogenicity (HAI assay)**  
of HD QIV versus the HD TIV which does not contain the corresponding B strain

**3 Assessment of Safety**  
similar safety profile of HV QIV-HD versus TIV-HD

**All were met**  
*(geometric mean titre results next slide)*

**Note:** As agreed with FDA, non-inferiority criteria used margins of 1.5 for GMTs and 10% for seroconversion rates; superiority was demonstrated if 95% CI for the difference of the  $\log_{10}$  (GMT) for IIV4-HD vs. SD QIV was  $>\log_{10}(1.5)$  and for the difference of seroconversion rates was  $>10\%$ .

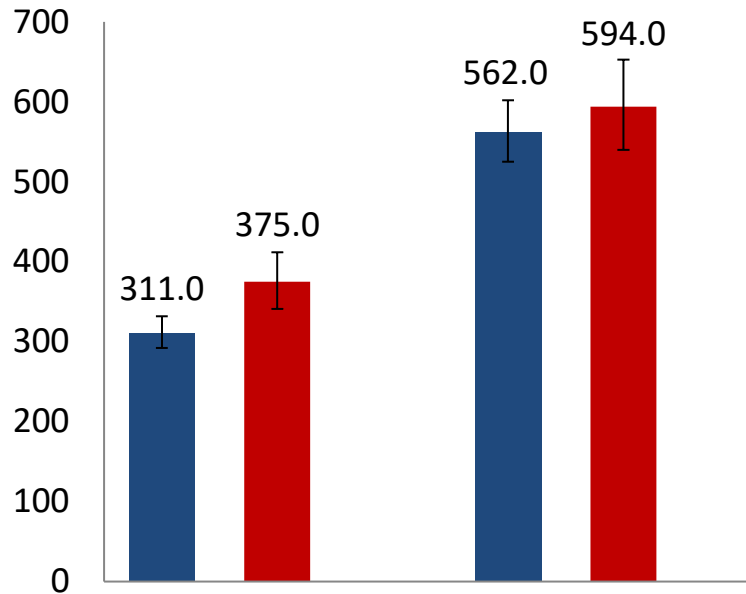
**Reference:** Chang et al. Vaccine 2019; 37: 5825-34

# IIV4-HD induced non-inferior geometric mean titre (GMT) for all 4 strains vs. IIV3-HD

## GMT, by study arm & strain\*

IIV4-HD

IIV3-HD (pooled GMTs from IIV3-HD1 & IIV3-HD2)



Similar results for seroconversion measure

### Notes

\* For simplification purpose, results for B lineages are not included in graph (available in publication by Chang et al.)

† Lower bound of the confidence interval (CI) should be >0.667 for non-inferiority to be reached

Reference: Chang et al. Vaccine 2019; 37: 5825-5834

Abbreviations: CI=confidence interval; IIV4-HD=high dose quadrivalent influenza vaccine; IIV3-HD=high dose trivalent influenza vaccine

	A/H1N1	A/H3N2
Ratio of GMT	0.83	0.95
Lower bound of the CI*	0.742	0.841



# Key learnings: IIV3-HD → IIV4-HD

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## Influenza vaccines

↑ valency with emergence of new strains

**Path to licensure: comparing with standard of care**

## IIV3-HD

↑ antibody response  
→ accelerated licensure → post-licensure efficacy trial

**Early access to better vaccine is important**

## IIV4-HD licensed via immunobridging approach

**No additional efficacy trial required** (*given the proven clinical benefits of IIV3-HD*)

**Placeholder: Moderna COVID-19 vaccines**

# WHO support to regulatory preparedness



COVAX Workshop

Multivalent COVID-19 vaccines to help address emergence of variants: CMC and Clinical implications

14 April 2021

David Wood / Regulation and Prequalification, WHO

# WHO is developing an integrated approach to monitoring/assessing SARS-CoV-2 variants



# 29 March 2021 WHO Consultation

## Session 3: Impact on public health decision-making

Regulators have already developed national or regional guidance on evaluation of changes, if needed, to COVID-19 vaccines with established vaccine efficacy

- US FDA, EMA, ACCESS consortium (Australia, Canada, Singapore, Switzerland, UK) have guidance

For pandemic control, need a global approach

- WHO published guidance for PQ/EUL assessments
- [https://extranet.who.int/pqweb/sites/default/files/documents/Addendum\\_Evaluation\\_Modified\\_Covid-19\\_Vaccine.pdf](https://extranet.who.int/pqweb/sites/default/files/documents/Addendum_Evaluation_Modified_Covid-19_Vaccine.pdf)
- WHO will support mechanisms to foster global convergence

Speed is critical for developers

- Need to accelerate evidence generation for existing, modified, new vaccines
- Rapid assessment and declaration of a VOC will accelerate the development process

Need rapid development of global standards

# For candidate vaccines that are still in development additional guidance is required

- WHO will modify its Target Product Profile based on global public health considerations to guide what is needed
- ACCESS and EMA guidelines already provide some guidance for multivalent COVID vaccines
- Regulators have recognized the need that additional regulatory guidance is required for candidate vaccines that are still in development and are actively working on guidance for new vaccines



# Issues for multivalent vaccines that will be considered by regulators

## Clinical issues

- Risk of immunological interference. Need to demonstrate the immunological response to the first antigen is undeterred by the addition of the additional type(s).
- How to benchmark the response to the new antigen against the response of the prototype vaccine antigen.
- Safety: the impact of potentially increased antigen amount versus the risk of reduced-dosing failing non-inferiority.

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## CMC issues

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Impact of multivalent formulations on potency assays and setting release specifications

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Impact on formulation and stability

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The difference between multiple DS that are blended together and multiple antigens in a single DS

# Also need to consider possible scenarios for clinical studies for candidate vaccines that are still in development

Placebo-controlled clinical efficacy studies are still possible

If placebo-controlled trials are no longer feasible, study designs that enable randomization to be maintained and clinical outcomes to be maintained are possible

- Guidance needed on choice of comparator, endpoints, margins and minimum threshold for acceptability if non-inferiority designs used

Clinical immunobridging studies to generate reliable evidence for authorization could be used in some situations

- Guidance needed on immune markers predictive of protection

Potential role for human challenge studies





# WHO support to regulatory preparedness

## Global Standards

- Multiple written standards are available, including
  - Technical Report Series 1004, Annex 9, Clinical Evaluation of Vaccines
  - TRS 1028, Annex 2, Guidelines on the quality, safety and efficacy of plasmid DNA vaccines
  - TRS 1011, Annex 2, Guidelines on Ebola vaccines
  - WHO guidance on mRNA vaccines for prevention of infectious diseases, *in development*
- Reference preparations
  - International Reference Panel and the first WHO International Antibody Standard for assay calibration

## Naming of COVID-19 Vaccines

- International non-proprietary names (INN) have been assigned to mRNA-based COVID-19 vaccines and plasmid-based DNA COVID-19 vaccine candidates
- Accelerated process and nomenclature scheme for vaccines for variants to be announced
  - See [INN Request form](#)



# WHO support to regulatory preparedness

- Prequalification and Emergency Use Listing procedure
  - WHO has placed into the public domain the status of COVID-19 vaccines for which an expression of interest has been received by WHO/PQ
    - Please visit the site regularly for the [latest updated version](#).
  - Guidance for PQ/EUL assessments
  - [https://extranet.who.int/pqweb/sites/default/files/documents/Addendum\\_Evaluation\\_Modified\\_Covid-19\\_Vaccine.pdf](https://extranet.who.int/pqweb/sites/default/files/documents/Addendum_Evaluation_Modified_Covid-19_Vaccine.pdf)
- Regulatory support to countries
  - >100 countries supported to issue regulatory authorizations for vaccines supplied through the COVAX Facility



# Key messages

- A globally coordinated response is essential for
  - identifying variants of concern,
  - their impact on vaccines, and
  - any modifications to vaccine composition
- Regulatory alignment to assess modifications to SARS CoV-2 vaccines with established efficacy is largely achieved – but detailed guidance on multivalent vaccines not yet provided
- Further regulatory guidance is being developed
- Careful messaging is essential so as not to disturb public trust in COVID-19 vaccines



## Closing remarks

- Thank you all for your participation and engagement today
- Workshop report will be distributed shortly to summarize today's conversation
- We will continue to share resources at the website here: [Epihub Link](#)
- Please consider sharing your thoughts and suggestions on this and/or future workshop in our Discussion Forum: [Link](#)
  
- **Other COVAX workshops:**
  - April 16 COVAX Enabling Sciences Workshop: Global and local approaches to detect and interpret SARS-CoV-2 variants
  - April 28 Vaccine Safety workshop: COVID 19 Vaccines Risk Management Planning: Stakeholders Experiences and Perspectives
  - Mid-May (TBC) -- COVAX Clinical Development and Operations Workshop
- The COVAX Manufacturing and Clinical SWAT Teams plan to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines

# COVAX

CEPI



**Thank you**