Best practices for tech transfer workshop

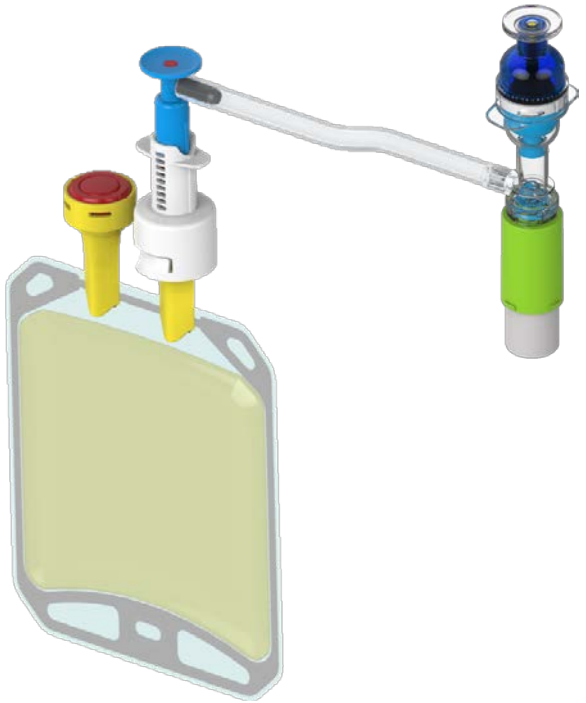
January 27, 2021

EOI announcement: Unit-dose syringe for pandemics

- Do you want to substantially increase your Drug Product capacity?
- And offer your users a prefilled-syringe-like ease of use? At low cost?
- Reduce your cold chain footprint by half?
- Or are you looking for an easy way to aseptically mix or dilute your product in the field?

CEPI and INTACT Solutions are developing a multidose prefilled syringe for pandemic response

- Usability: allows rapid mass vaccination with PFS-like ease of use
- Safety: sterility and dose accuracy assured
- Manufacturing: fast and flexible, cost effective with low cold chain footprint



We are looking for developers interested in using this technology for their vaccine product

- Expression of Interest open at https://cepi.net/get_involved/cfps/ with a deadline of **Sunday 28 February 2021, 15:00 CET**
- Or contact Renske.Hesselink@cepi.net

CEPI

INTACT within

INTACT Solutions

The Engineered Compliance

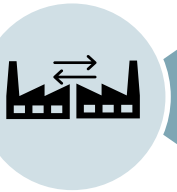
Agenda

Agenda:

- Introductions, meeting overview and rules – 5min
- Theoretical perspective: Samsung Biologics tech transfer process and protocols– *Andrew Kim, Samsung Biologics* - 20min
- ERVEBO® Vaccine for Ebola Virus – A Case Study on Approaches to Accelerate Process Development and Tech Transfer – *Joseph Califano, Merck* – 20min
- Case Study: Process AZ Flu vaccine – *Christian McLarnon-Riches, AstraZeneca* – 20min
- Industry Position: Impact of evolving analytical strategies on comparability, specification and National Control Laboratories testing – *Cristiana Campa, GSK* – 30min
- Regulatory perspective: NRA and WHO PQ – *Carmen Rodriguez Hernandez, WHO* - 20min
- Meeting close – 5 min

Tech transfer workshop: Introduction

Aspects of Technology Transfer for COVID-19 vaccines that will make the process more complicated:



Number of planned tech transfers is much larger than for other products

Many of the planned tech transfers will be from pharma originators to regional manufacturer recipients. High potential for miscommunications and misunderstandings due to differences in culture, experience base and language.

Limited time to predict demand and build the capacity of production components

High demand increases pressure/need for getting everything right the first time

Tech transfer workshop: Introduction

Aspects of Technology Transfer for COVID-19 vaccines that will make the process more complicated:

Initial tech transfer activities will take place during the pandemic

- Travel will be limited. Quarantine requirements may dictate remaining in place once people have arrived at a site
- Access to certain resources (e.g. bags, resins, vials) will remain difficult for much of 2021
- New waves of infection may impact staffing levels, which could slow down or stop tech transfer activities

Many countries will be depending upon supply arising from new manufacturers, who are the tech transfer recipients. Potential delays/failures could impact ability to initiate or complete immunization country or regional campaigns.

Limited time to gain process and product knowledge during development, and use of new platforms, may impact the ability to characterize the transferred process & product relative to the originator's process/product

Theoretical Considerations: Samsung Biologics Tech Transfer Process and Protocols

Andrew Kim, Associate Director, DSP MSAT
Samsung Biologics
COVAX Tech Transfer Workshop, 27 January 2021

SAMSUNG BIOLOGICS

Overview of Samsung Manufacturing Facilities

Validation completed in all three plants and currently in operation.

Plant 1 (2011 - 2013)

Cell culture capacity	30,000L x6 5K
Fill finish	• Liquid & Lyo vials
cGMP ready	• cGMP operation from June 2013
Laboratories	• QC laboratory • PD lab expansion in Plant 2

Plant 2 (2013 - 2016)

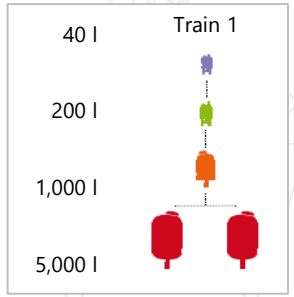
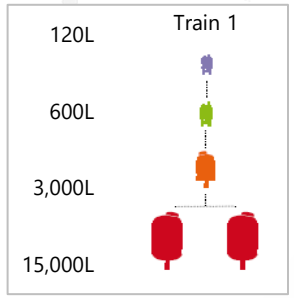
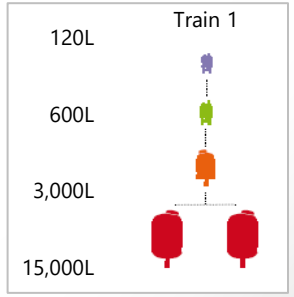
Cell culture capacity	154,000L x10 15K x2 1K Single-Use x2 1K Stainless Steel
Fill finish	• Liquid vials (Lyo TBD)
cGMP ready	• cGMP operation from Feb. 2016
Laboratories	• QC lab expansion in Plant 1 • PD laboratories

Plant 3 (2015 - 2018)

Cell culture capacity	180,000L x12 15K
Technology	• Fed-Batch with N-1 Perfusion capability
cGMP ready	• cGMP operation from Oct. 2018
Laboratories	• QC laboratory • PD laboratories

All 3 plants are cGMP compliant with a dedicated Quality Control Lab & Process Development Unit

Capacities & Arrangement

3 Trains with scale-up ratio of 5x	
5 Trains with scale-up ratio of 5x	
6 Trains with scale-up ratio of 5x	

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*NOTE: Single-use bioreactors to be operational in Q1 2020

Presentation Overview

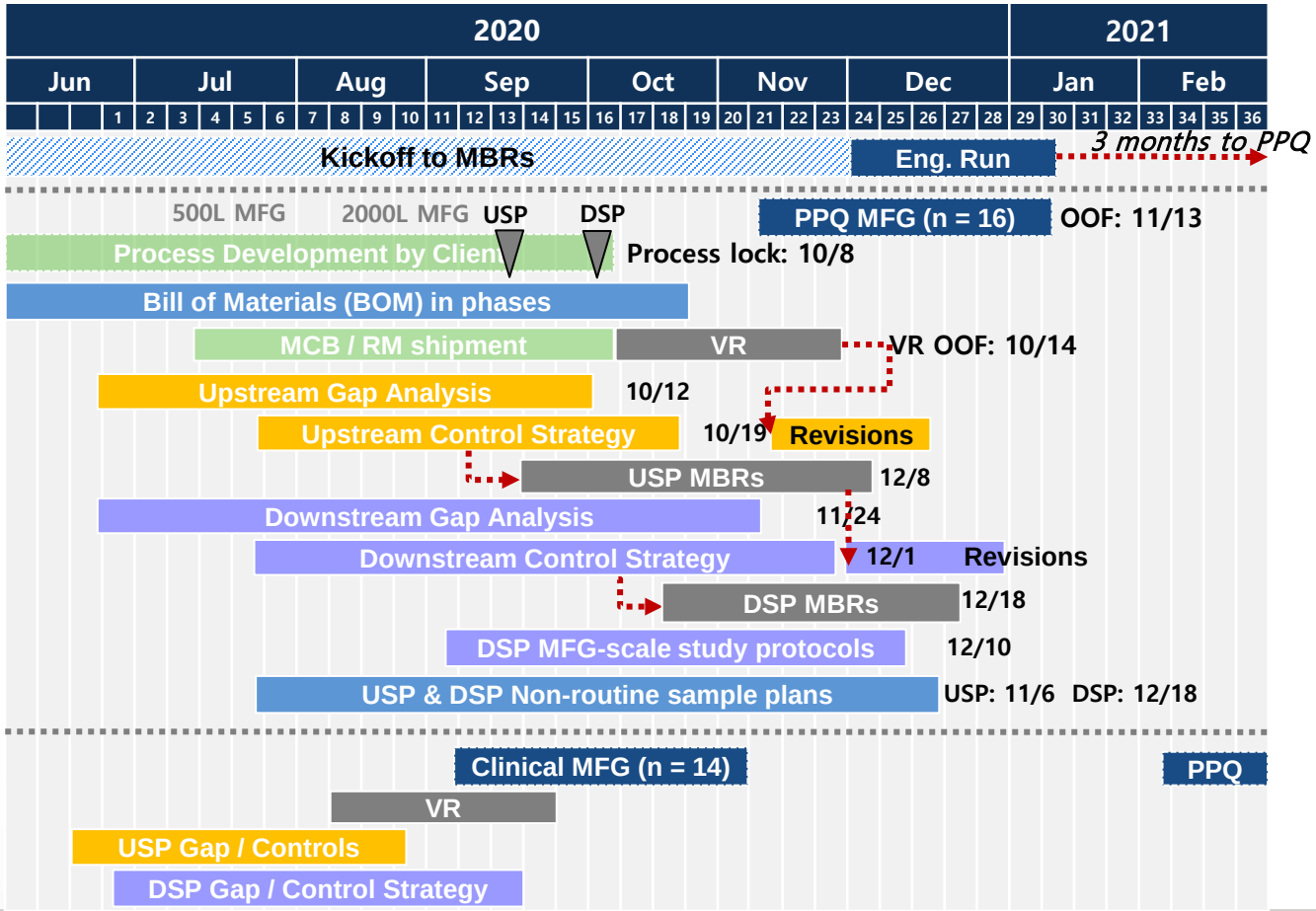
Objective: **Share SBL's learnings and best practices to accelerate tech transfer** *(focus on manufacturing process)*

- Introduce expedited tech transfer at SBL for COVID-19 antibody projects
- Summary of key acceleration components
- Laying a foundation in team logistics and project governance
- Managing tech transfer activities
- Unique COVID-19 challenges
- Risk mitigation strategies
- Next steps

- Reference: https://www.bioprocessonline.com/doc/best-practices-for-biopharmaceutical-technology-transfer-facility-fit-and-process-gap-assessments-0001

Accelerated COVID-19 Programs at SBL

- **Typical SBL timeline for tech transfer is 6 months from kickoff to vial thaw (engineering run)**
  - ***COVID-19 program challenges*: no engineering runs & critical activities performed in parallel**



Baseline

- Control strategy completed 1 month before OOF (vial thaw)

Project A: 5 months transfer →PPQ

- Process development during tech transfer (client 2kL data)
- Bill of materials documents written in phases (long lead items first)

Project B: 3 months transfer →Clinical

- Client drop shipment of critical RMs
- Control strategy documents written in phases (buffers/media first, etc.)

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Tech Transfer Timeline Acceleration

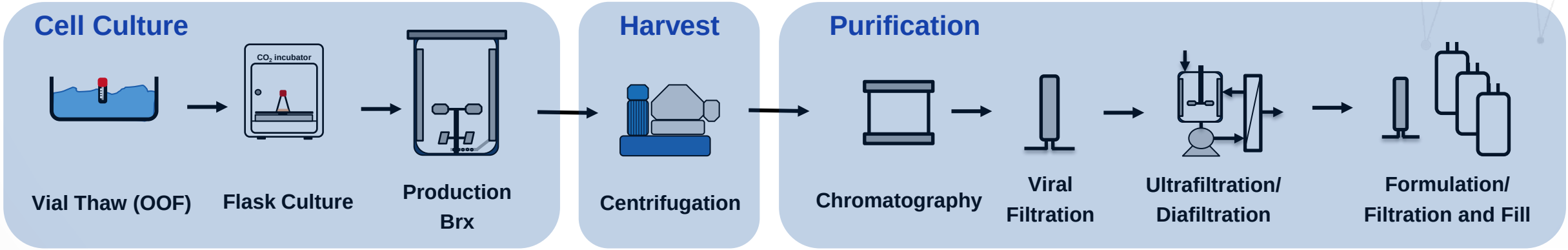
SU: Sending unit
RU: Receiving unit

- **Emphasis on early assessment to identify critical gaps**
- **Supply chain gaps prioritized and continuously monitored**

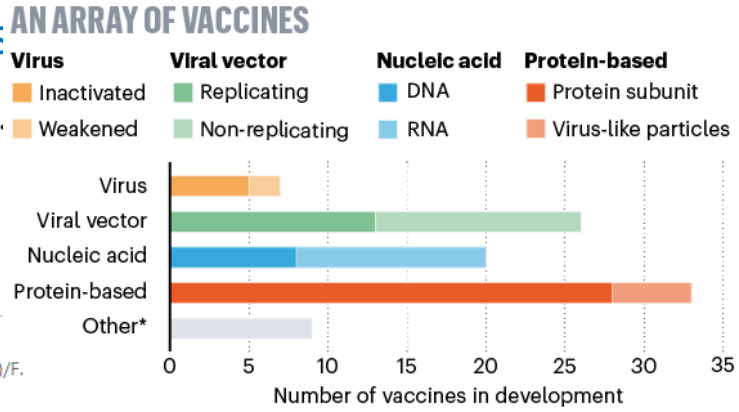
Traditional Components	Sending site	Receiving site
Careful planning & Clear communication	+	++
Strong technical expertise	++	++
Facility and equipment considerations → identify gaps, develop mitigation plans	+	++
Acceleration Components	**Sending site**	**Receiving site**
Accept that traditional process development timelines may not be suitable	++	
Platform production process and standardized procedures	+	++
Phase structured approach to meet manufacturing needs	++	++
Expedited assessment of facility and process fit to identify critical path items	+	+++
Supply chain risk: order long lead items immediately, assess alternatives	+++	+++

Key Difference for Antibody vs. Vaccine Manufacture

- Accelerated tech transfer enabled by an established manufacturing platform
- Established antibody manufacturing platforms → consistent and reliable scale-up
  - Understanding of technical challenges and critical parameters
  - Common elements: CHO cells, defined and consistent growth media, standardized analytical technologies, consistent purification process, cumulative experience in working with the production platform



- A vaccine manufacturing platform is not established (need >6 platforms
  - Wide range of vaccine types (attenuated, purified proteins, DNA-encoded, etc.
  - Bioassays for determining CQAs for specific vaccines remain proprietary



Sources: *Nature* analysis based on: WHO COVID-19 Vaccine Landscape/Milken Institute COVID-19 Treatment and Vaccine Tracker/T. Thanh Le *et al. Nature Rev. Drug. Disc.* http://doi.org/ggrnbr (2020)/F. Amanat & F. Krammer *Immunity* **52**, 583–589 (2020)/W. Shang *et al. npj Vaccines* **5**, 18 (2020).

Preventing Miscommunications

- **Clear communication is of critical importance: misunderstandings lead to delays and rework**

- **Overcoming communication challenges at Samsung:**
  - Cultural differences (Korean versus American, Korean versus European)
    - SBL technical stewards can bridge Western and Eastern cultures (expats from Western countries)
  - Language differences (various English capabilities on SBL side, accented English on client side)
    - SBL personnel with strong English skills (educated in western universities) facilitate meetings
    - Supported by technical stewards who ensure smooth communication and oversee technical activities
    - Teams confirm alignment via powerpoint slides and emails; critical decisions documented by client memorandums
  - Experience gap (average age of SBL employee is 28 years old)
    - Technical stewards ensure sound science and quality risk management (10+ years biopharma experience)
    - Client technical expertise provides additional oversight
    - Don't reinvent the wheel for the same type of problem across different projects & anticipate common issues
      - Example: re-use powerpoint slides and talking points for control strategy discussions (e.g., how to handle non-key parameter excursions)

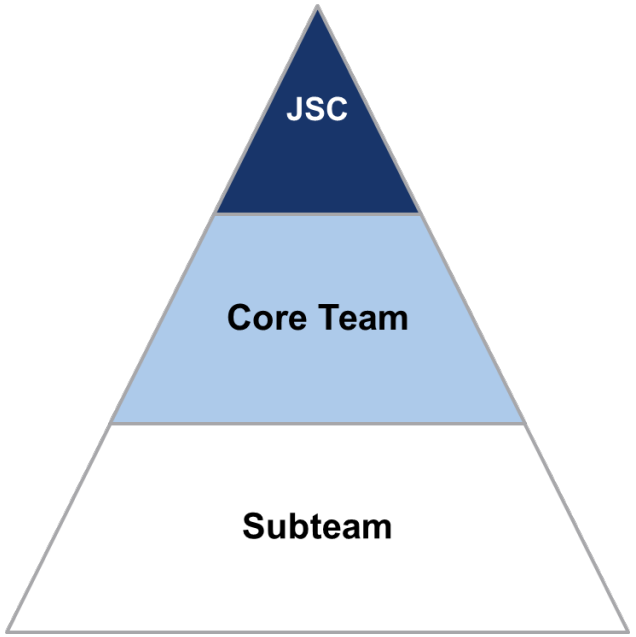
Team Logistics and Project Governance

- Strong teamwork based on collaborative attitude & clear communication

- Decision makers clearly identified to prevent delays
- Consider interconnections in matrix team structure (ensure appropriate decision-makers are engaged)
- Document coordinator (SU) to serve as primary contact for managing document review timelines

- Core functional areas have a single point of contact:

Project Management	Project management (serve as HQ, attend all meetings)
Technical	Manufacturing sciences and technology, Manufacturing (CC, PP)
Quality	Quality assurance, Quality control
Procurement	Supply chain, material management (warehouse)



Overall Strategy and Business Critical Decisions
- Final decision makers for Business, Operation, Quality

Key Milestones and Decisions
- Ensure key milestones are achieved on time
- Decision on technical issues / resolve issues for subteam

Plan and Execute Daily Activities
- SMEs Responsible for execution of project activities
- Escalate to core team for timely decision making
- Report progress to core team

Meeting frequency:

JSC on an as-needed basis
Core team – monthly
Subteams – weekly (ad-hoc for emergencies)

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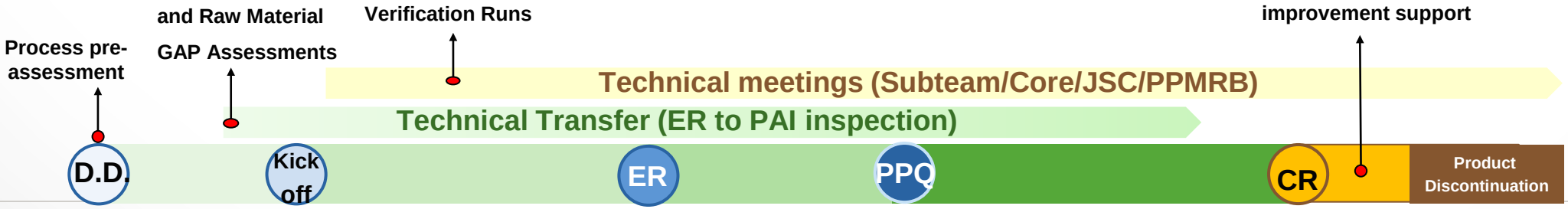
Tech Transfer Activities and Risk Identification

- **Careful orchestration of parallel activities depends on solid understanding of the key deliverables**
  - Key deliverables: Process description → Control strategy → Manufacturing batch records
    - SU: Immediate delivery of client tech transfer documents (rolling format if necessary)
    - RU: Generate a document flowchart to visualize document review process (& identify predecessor documents)
  - Continuously monitor critical path (dependent on drop dead dates)
  - Seek "Right first time" quality in deliverables to minimize rework and delays

Step #1!!! immediately	Perform mass balance to identify equipment/RM gaps and address	
Receiving site	Know the equipment and facility	Consider common tech transfer issues
Sending site	Consider manufacturability of operating ranges	Focus on critical needs



Unique COVID-19 Challenges

- **CAPEX bottleneck:** (12 to 18 months) procurement or drop ship must meet manufacturing timeline
- **Supply chain risk (raw materials, consumables)**
  - Assume worst case quantities for production and facility fit gaps
  - Identify high risk items early. Mitigate with alternative materials (lower performance) or client perform RM release testing
    - Example: Long lead items require 4 to 6 months, RM release testing method transfer can require up to 4 months
    - Example: Use Asahi Kasei Planova filters due to Merck Vpro supply issues, run operation slower using fewer filters
- **No face-to-face interactions & stringent anti-COVID measures to prevent business slowdown**
  - All virtual meetings using Zoom or an appropriate tool
  - Baseline is no Person-in-Plant presence during production
    - Potential options: Google glass tool for virtual presence, SU hire a SME to support tech transfer
    - Minimum requirement: 24 hour availability of SU SMEs to enable quick response to production issues
- **Handling regulatory feedback under a tight timeline**
  - SU responsible for understanding program regulatory requirements
  - RU focus on scaling up production and meeting communicated regulatory needs

Risk Mitigation Strategies (Non-supply chain)

- **Plan mfg-scale wet runs to de-risk key equipment gaps**
  - Example: SBL performed a wet run to test UF operation using a 1000L mobile vessel (versus the skid 750L tank)
- **Plan supporting studies (SU or RU) to modify operating ranges that present risk**
  - Examples: widen the conductivity range for preparation of a process buffer (to ±2 mS/cm) or perform a one factor experiment to increase ultrafiltration concentration target from 100 to 120 g/L to fit vessel constraint
- **Identify key discussion items early to avoid rushed decision-making**
  - Alignment between SU and RU on control strategy terminology and quality response to deviations
    - Example: resolve differences in definitions of shared terms (e.g., acceptable range) or what is/is not a deviation
- **Prepare for the worst: make troubleshooting easier**
  - Verification run (small-scale): identify process challenges early, useful to troubleshoot mfg-scale issues
  - Leverage SU historical data (SU facility, platform process)
- **Generate a campaign playbook before first batch**
  - RU identify potential or common issues for first-time manufacturing (e.g., filter clogging, high pressure in chromatography) and planned responses

Campaign Playbook (Example)

No	Category	Classification	Risk	Action	Severity	Likelihood
1	General	Packing	Fail column integrity test (HETP and Asymmetry)	Repack	Low	Low
2		Intermediate hold time	Exceed hold time	Contact MSAT if hold time is expected to be exceeded due to process delay. * If hold time is already exceeded, pause process and contact MSAT.	Medium	Medium
3		Depth filter	Insufficient Flush	Perform more flush	Low	Low
4		Linear velocity	Linear velocity exceeds specified set point	There's no lower limit so reduce velocity while making sure pressure stays within range.	Low	Low
5		Membrane or filter clogging	Filter clogged during loading	Pause process -> replace with new filters -> resume process with remaining product * product that was left in the filters/membrane will be drained. * Re-equilibration is required for depth filters.	Medium	Low
6		Effluent pH and/or conductivity	Fail to meet pH and/or conductivity specifications	Perform 1 more CV or additional Flush -> re-check pH and conductivity * if fail to meet pH and/or conductivity after additional flush, contact MSAT	Low	Low
7		Load cycles	Calculation shows that more than the maximum number of cycles is necessary *ProA: Max 5 cycles, AEX: Max 3 cycles, CEX: Max 4 cycles	Load product to meet max load ratio and drain excess product	Medium	Low
8		Elution	Collection does not start at expected collection volume *Expected ProA Collection Start: 0.7 - 1.0CV Expected AEX Collection Start: ~0.7CV Expected CEX Collection Start:: 1.0 - 1.1CV	Pause process -> contact MSAT * For E4A ProA, if end condition (0.03AU to 0.10AU) is met before 0.5 CV collection, stop collection manually.	High	Low
9		Pool	Pool does not meet specified pH and conductivity range	Contact MSAT to discuss next steps	Medium	Low
10		Sampling	Pool sample does not meet minimum volume requirement in vessel to sample (due to low titer, etc.)	Contact MSAT to discuss next steps * For Protein A, dilution up to 20% with elution buffer should be fine but should monitor pool pH and conductivity with in-line probe to confirm pH and conductivity is within the acceptable range during addition. After addition, pH and conductivity should be confirmed by off-line measurement. * For CEX, dilution is fine but need to monitor pH and conductivity with in-line during addition. After addition, pH and conductivity should be confirmed by off-line measurement.	Medium	Low
11	ProA	Loading temperature	Transfer HCCF to DSP area before reaching room temperature.	Pause process -> drain what's already been transferred -> wait until Harvest heats to room temp. *Inform upstream 8 hours before ProA load starts	Low	Low

Recommendations and Next Steps

Before tech transfer kick-off…

- Prepare ahead of tech transfer kick-off (order common RMs, create document templates, etc)
- Shorter duration of tech transfer increases risk
  - Initiate tech transfer as soon as possible (even with limited resources) to focus on critical path items earlier

During tech transfer…

- Draft a comprehensive project timeline with rational drop dead dates for critical activities
  - Plan activities in parallel wherever necessary
- Identify key decision makers early to ensure smooth communication
- Prioritize basic facility fit assessment as step #1 to identify critical long lead items
  - Or identify equipment and raw materials that require alternatives
- Act with appropriate urgency and escalate issues immediately
- Develop risk mitigation plans in a timely manner
  - Proactively identify issues that may require lengthy discussion (e.g., control strategy philosophy)
- Identify “high potential” manufacturing issues and devise appropriate response plans

Lessons Learned

Critical bottleneck: Limited supply of raw materials and consumables

- Kick off tech transfer immediately for sole purpose of initiating procurement of materials or equipment
- Don’t hesitate to escalate supply issues to provide more time for technical teams to find alternatives

Work smarter, not harder: Common issues will arise for similar tech transfers

- Don’t waste time reinventing the wheel – proactively address issues across projects
  - Responsibility rests more on pharma originators for vaccine tech transfers (versus SBL case)

GOOD LUCK!!!

For questions, feel free to contact:
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(LinkedIn) www.linkedin.com/in/andrew-kim-1aba6149

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Ervebo® vaccine for Ebola virus – a case study on approaches to accelerate process development and tech transfer

Joseph P. Califano, PhD

Vaccine Process Development & Commercialization

January 27, 2021

Outline

Background

- Ebola virus and outbreak
- Ervebo® vaccine

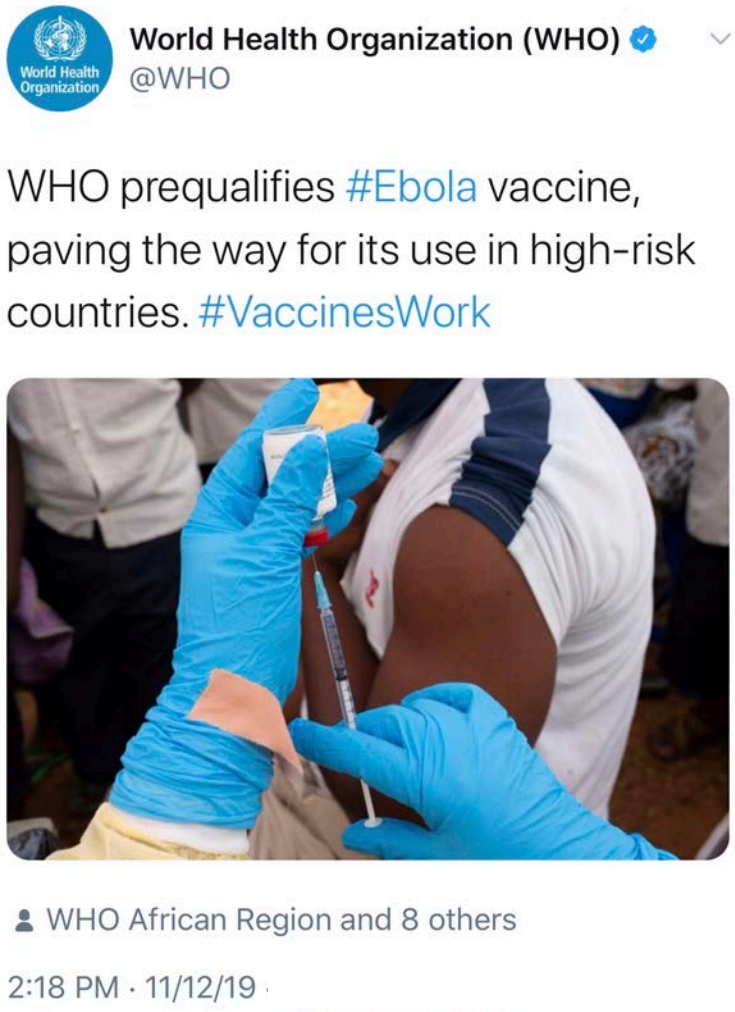
Development and Tech Transfer

-Analytical comparability

-Approaches to accelerate

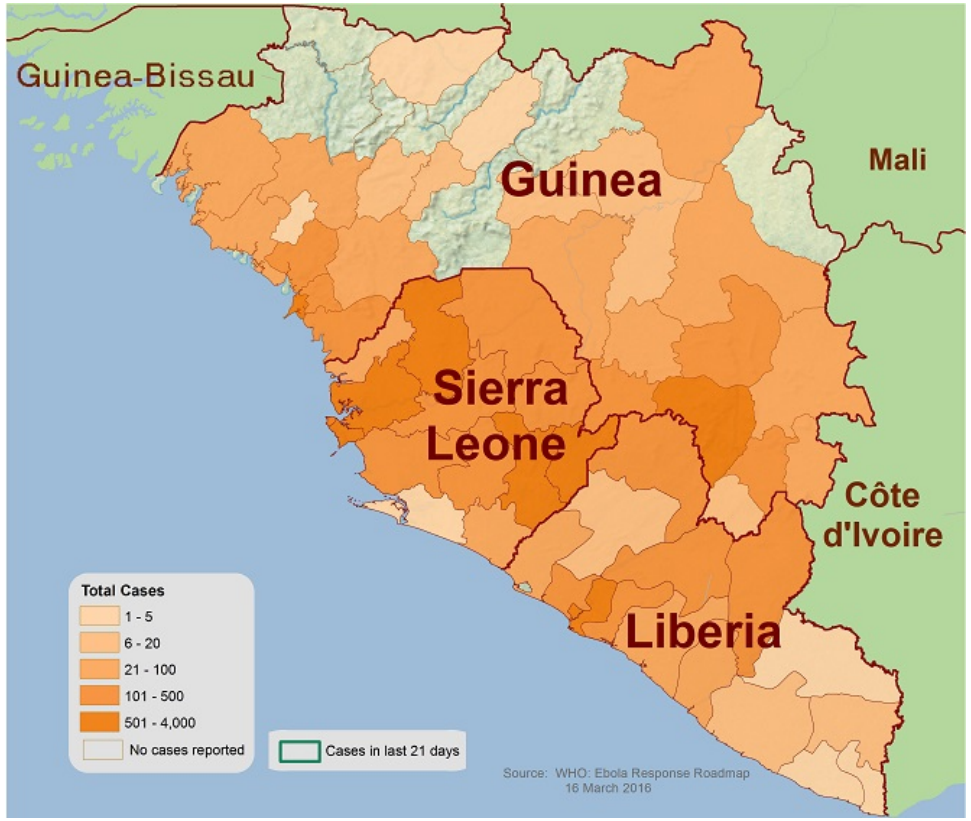
-Challenges

Key Takeaways



2014-2016 Outbreak

Total Cases as of 16Mar2016 (latest update)



World Health Organization:
"The 2014–2016 outbreak in West Africa was the **largest and most complex Ebola outbreak** since the virus was first discovered in 1976.
There were more cases and deaths in this outbreak than all others combined."

- >11X larger than all previous outbreaks combined
  - >11k deaths
- $2.2B in GDP lost in Guinea, Liberia, Sierra Leone in 2015
- >$3.6B spent to fight the epidemic by the end of 2015

https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/distribution-map.html

https://www.cdc.gov/vhf/ebola/pdf/impact-ebola-economy.pdf

Ervebo® (Ebola Zaire Vaccine, Live), A Very Brief Timeline

2014

- Initial development by Public Health Agency of Canada; in-licensed from NewLink Genetics
- **MSD** assumed responsibility to research, develop, manufacture, and distribute the candidate vaccine

Feb 2017

- First evidence of efficacy in human subjects for any Ebola vaccine

Nov-Dec 2019

- FDA approval
- WHO Pre-Qualification
- EMA conditional marketing authorization
- First African registrations

References: European Commission. Vaccine against Ebola: Commission grants first -ever market authorisation. European Commission Web site. https://ec.europa.eu/cyprus/news/20191112_en; World Health Organization. WHO prequalifies Ebola vaccine, paving the way for its use in high-risk countries. World Health Organization Web site. https://www.who.int/news -room/detail/12-11-2019-who-prequalifies-ebola-vaccine-paving-the-way-for-its-use-in-high-risk-countries; https://www.popsci.com/best-of-whats-new-2015/healthcare

Development and Tech Transfer Challenges and Goals

Parallel activities to drive program forward with speed

Short Time-Lines

Rapidly evolving external environment

New approaches were needed to accelerate development and tech transfer

Fully define and transfer a robust manufacturing process:

- Process development and scale-up
- Process characterization
- Emergency-Use dose manufacturing
- Tech Transfer to international commercial site
- Process Performance Qualification
- Support marketing application

Approach to Analytical Comparability

Establish analytical comparability *retrospectively* between the **original clinical batches** from CMO and the **scale-up Pilot Plant batches** to

1) Determine feasibility of scale-up
2) Set prospective criteria for formal commercial comparability

1. Contract Manufacturing Org

-Clinical Dose Manufacturing

2. Biologics Pilot Plant

-Scale-up to commercial scale
-Emergency Use/Clinical dose Manufacturing

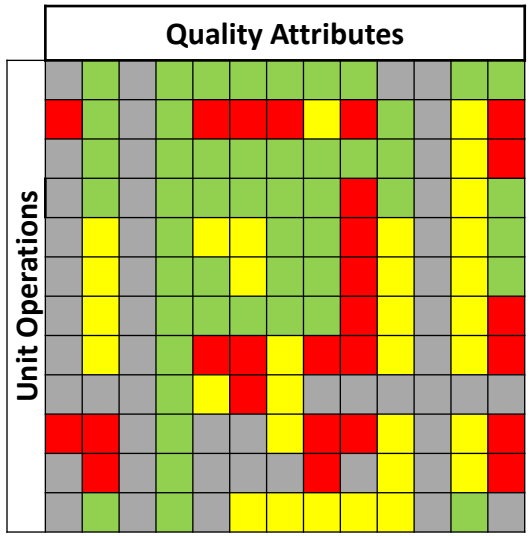
3. Commercial

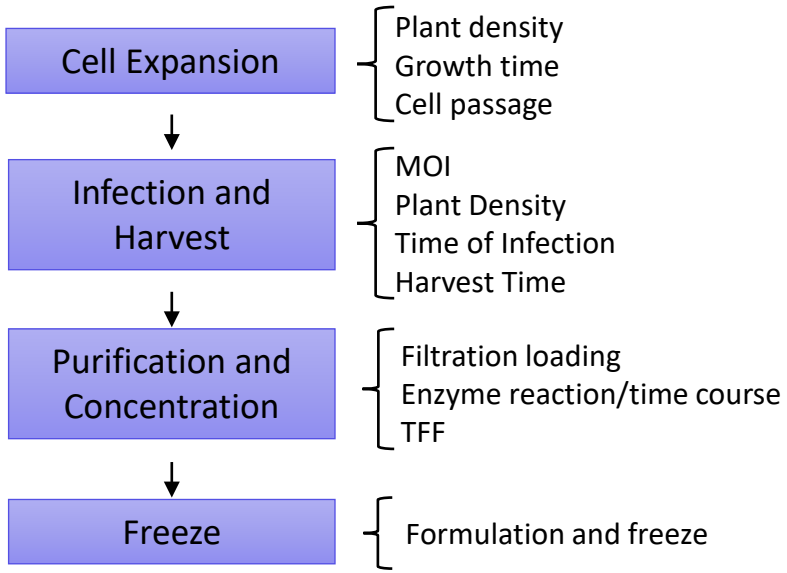
-Process characterization
-Transfer from pilot plant to commercial site
-PPQ and Commercial batches

Formal, *prospective* comparability protocol to establish analytical comparability between the **PPQ batches** at the commercial site and the original **clinical batches** from the CMO

Approaches to Accelerate

Use a Risk-Based Approach to Prioritize Experiments; Leverage Prior Knowledge



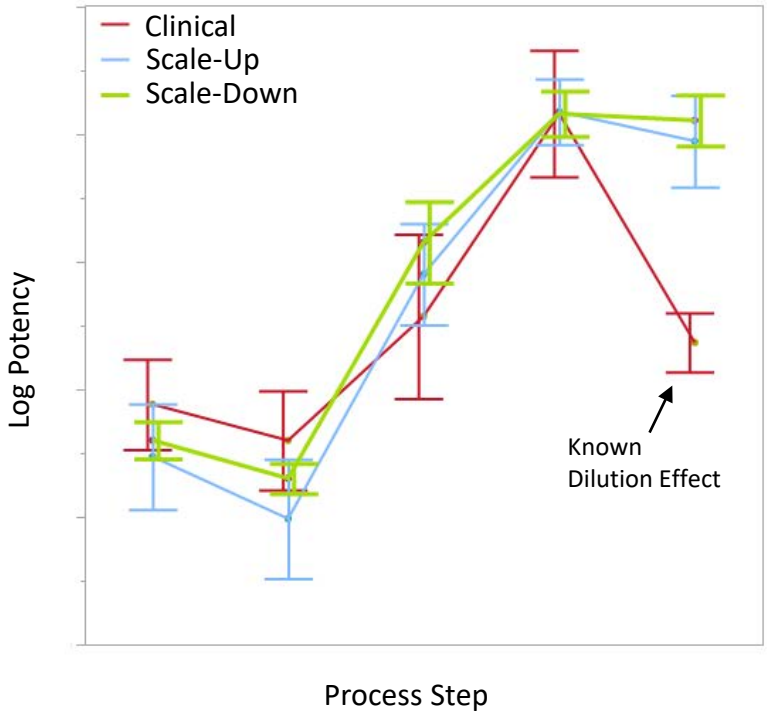


- A team of live viral vaccine SMEs evaluated the clinical manufacturing process with a risk assessment to help identify unit operations and process parameters in need of study
- Unit operations and parameters at **high risk** or with **little understanding** were prioritized

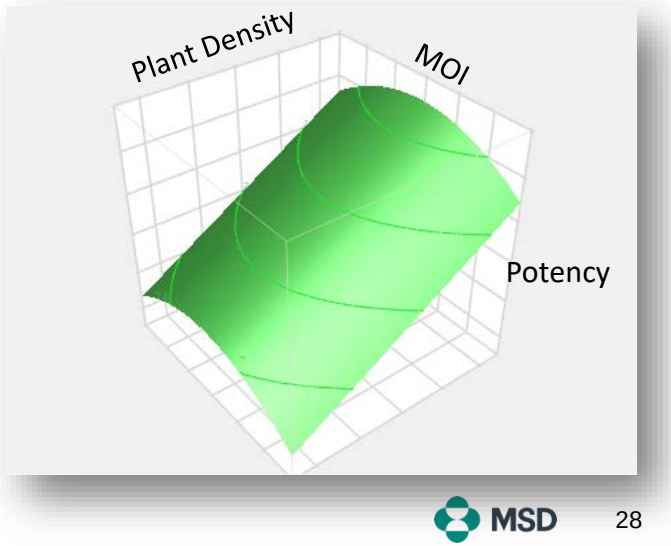
MOI, multiplicity of infection
TFF, tangential flow filtration

Approaches to Accelerate

Develop a Scale-Down Model for Experimental Work



- Reduced cycle time to generate data from 8+ weeks to 3 weeks
  - ➢ Created a lab cell bank for high-throughput studies
  - ➢ Reduced purification process volume from 80L to 1L
- Demonstrated representative to full-scale and clinical batches, enabled DOE
  - ➢ Investigate parameter interactions



First draft of Manufacturing Process Description issued within 1 year of project start

Approaches to Accelerate

Develop a Single-Use Drug Substance Process

Layout Study

- Evaluate designs – obtain VOC
- Hands-on training and team building
- Assembly layout for process and area fit
- Seek to understand waste streams

VOC, voice of customer

Approaches to Accelerate

Develop a Single-Use Drug Substance Process

Month 0-5
- Design and scale-up
- Full scale ENG and GMP runs

Month 6
- PFD
- URS
- RFP

Month 7
- Initial Sourcing

Month 10-11
- Layout Study and functional evaluation

Month 10-13
- Refined designs with VOC

Month 14
- Signed-off on last component
- All orders placed

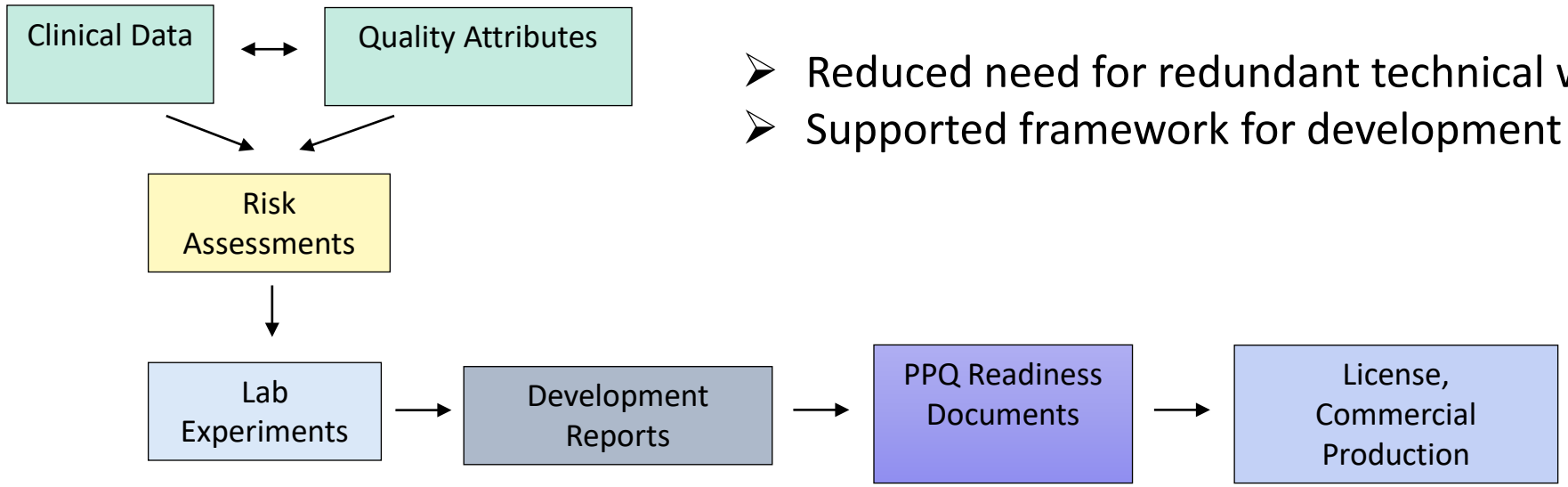
Month 15
- Components start to be delivered

PFD, process flow diagram
URS, user requirement specificatio
RFP, request for proposal
VOC, voice of customer

- Final process is 100% single-use
- >500 assemblies made from 42 modular designs
- Established a platform approach for future vaccines
- Allowed for rapid transfer to the manufacturing site (15 months)

Approaches to Accelerate

Write with the End in Mind



- Created a map of the documentation strategy with the marketing application in mind

➢ Reduced need for redundant technical writing
➢ Supported framework for development

Key Takeaways

Several approaches were used to accelerate process development and tech transfer of Ervebo®:

- Work in parallel
- Use a risk-based approach to prioritize studies
- Create and use a scale-down model to increase experiment throughput
- Implement a documentation strategy with the marketing application in mind
- Consider single-use solutions
- Manage knowledge transfer and “hypercare” support of PPQ and commercial manufacturing

Acknowledgements and Thanks

- Study volunteers and study investigators
- Our many external partners, collaborators, and funding organizations
- Ervebo® product development team, sub-teams, leadership
- This project has been funded in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201500002C, HHSO100201600031C, and HHSO100201700012C.

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Thank you!

Questions?

COVAX Workshop 27Jan2021

Influenza Vaccine Technology Transfer: A case Study

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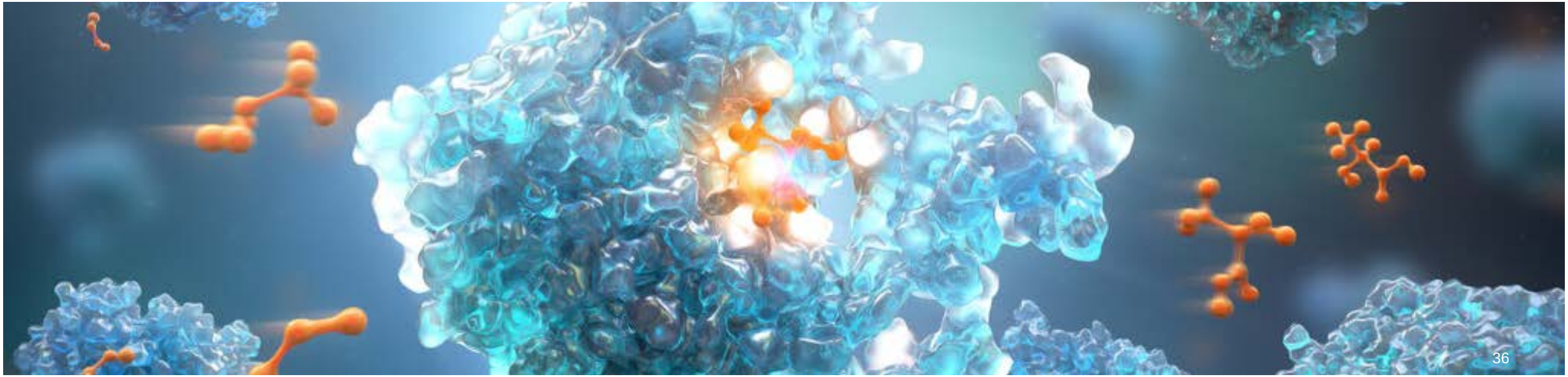
27Jan2021



Outline

- Background & Agility requirements, defining success
- Technology Transfer Approach
- Learnings & applications to other transfers

Influenza Vaccine Process Transfer

- Tech transfer and consolidation of all Live Attenuated Influenza Vaccine research, development, and GMP activities from US to the UK
  - Annual strain research and development processes
  - Annual strain selection business processes
  - GMP QC tests
  - Critical reagent generation and qualification
  - Process development
  - Analytical development
- The knowledge transfer of 10+ years of LAIV history
- Mission Critical to the future of the Influenza Vaccine franchise

Key elements for success

- Efficient tech transfer
  - Transfer of Influenza strain development manufacturing processes and methods
- Clear line of Sight
  - View of specific product plans and portfolio; facility plans
- Timing of Key Decisions
  - Decisions that impact CMC activities and other functions

Efficient & Agile Technology transfer

- Business Drivers
  - Keep CMC off the critical path to BLA or variation to existing licence
  - Speed to market
  - Balance capacity
  - Clinical drug supply for pivotal clinical trials
  - Several industry cases of lost opportunity or productivity due to poor tech transfers

- Range of Transfers
  - Drug Substance
  - Drug Product
  - Test Methods
    - Biochemical, Bioassays

- Techniques to reduce timelines and the resources needed to deliver right first time Technology Transfer

Agile Technology transfer

- Best practices and tools to deliver fast, lean, RFT tech transfers by
  - Planning and budgeting
  - Packaging the knowledge
  - Organisation
  - Controls, gates and handovers
  - Reviews and learning
  - Tools and templates

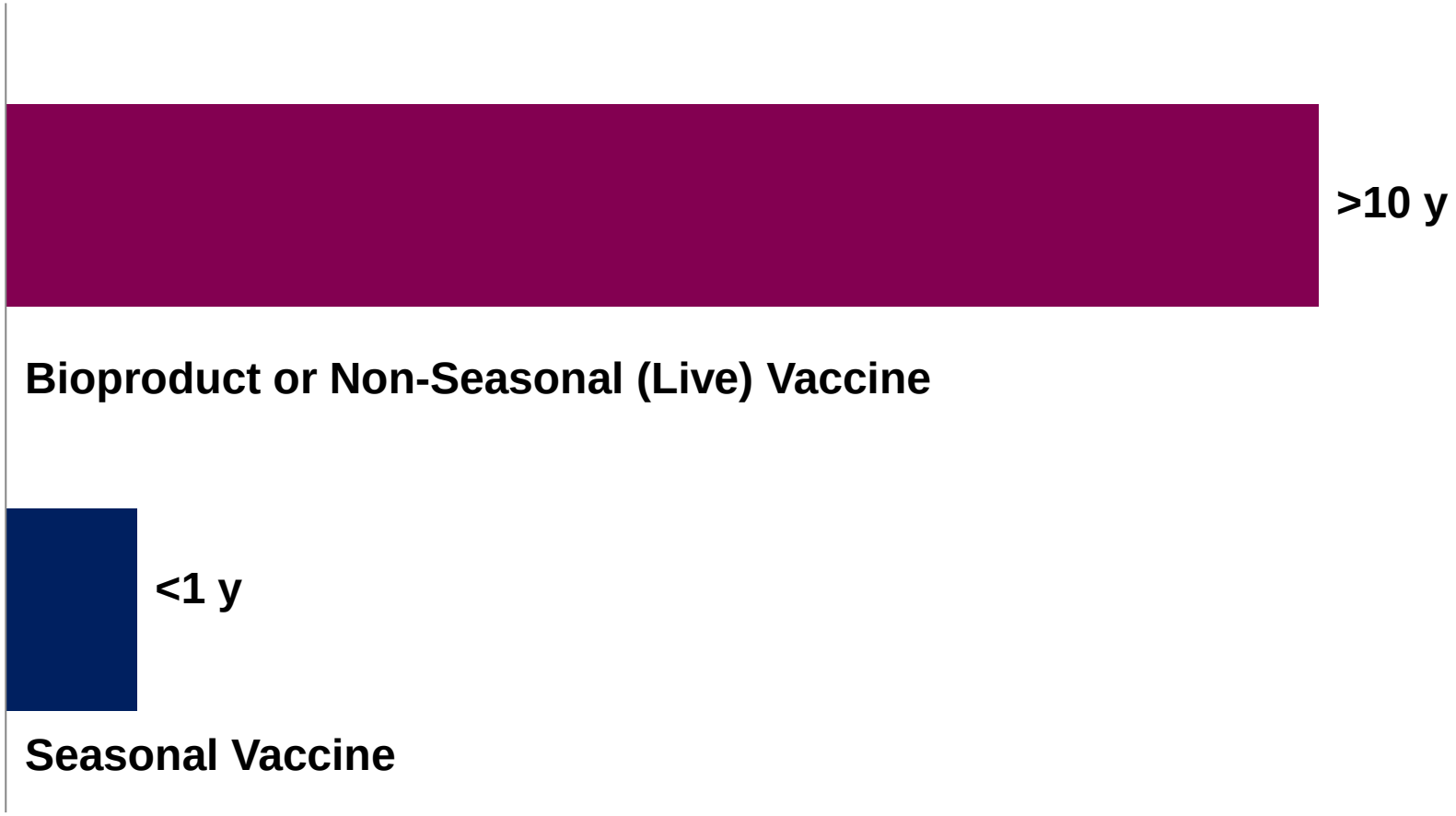
- Treat each transfer is an opportunity for improvement over the previous

- Key goals for tech transfers
  - No engineering lots – (unless there is a technical reason) - saving people time (Dev & Ops) and cost
  - No longer than 6-months
  - High degree of collaboration - Improved team-work and trust
  - Defined roles / responsibilities
  - 20% reduced resource needs

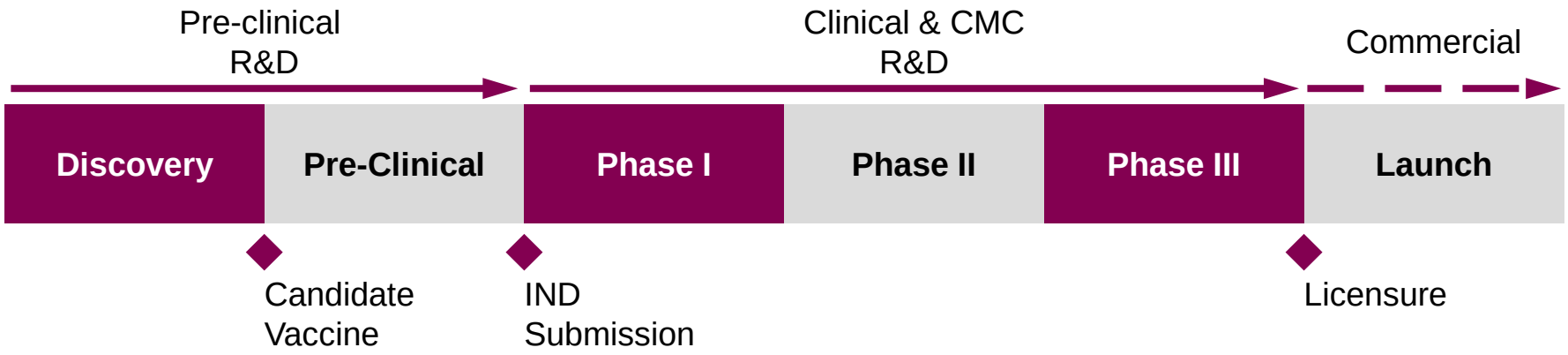
Lessons Learned from previous tech transfers

- Clearer definition of roles
- Decision making (Tech Transfer team vs. CMC team vs Development vs functional management)
- Better communication channels
- Better confidence in each others' skills / capabilities
- Takes too long to transfer / takes too much of people's time
- New product introductions could be simplified
- Solving facility constraints (water, tank volumes etc) would enable faster processing

A Compressed Timeline



Non-Seasonal (Live) Vaccine Development Timeline



A relatively long development time & lifecycle…

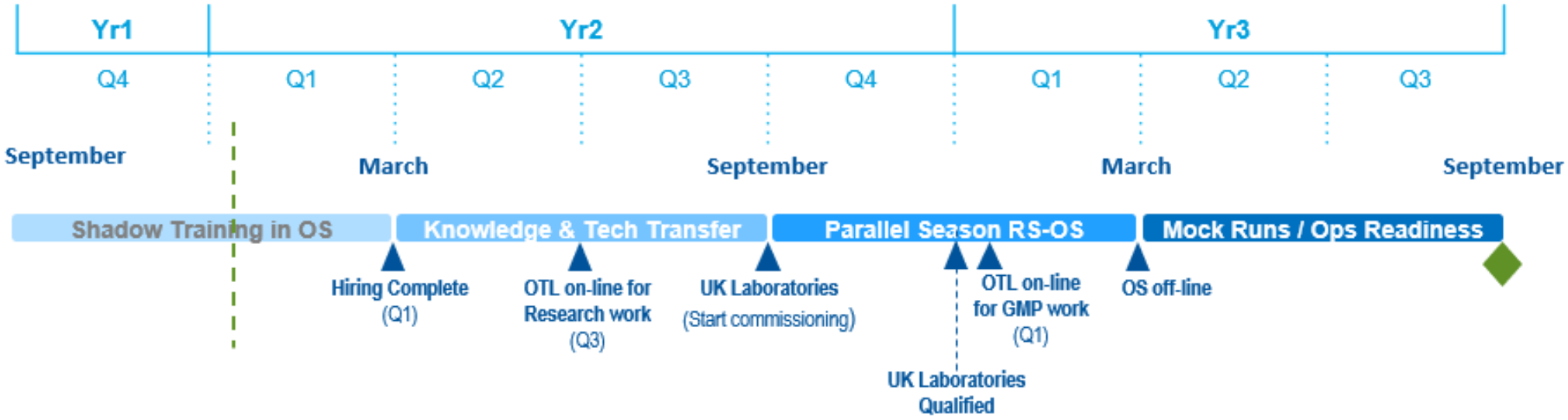
- >10 y from discovery to licensure
- >$800M cost to develop a *prophylactic* product[1,2]
- Clinical studies are large & complex
- Product on market for decades

Live Vaccine development time is compressed into ~5-6 months

[1] *J.A. DiMasi et al: The Price of Innovation. J. of Health Economics, 22 (2003), 151-185.*

[2] *Source URL: http://www.fiercebiotech.com/story/tufts-billions-wasted-pharma-rd-despite-new-biz-models/2013-01-08*

Technology Transfer Timeline



Annual Reformulation Challenge (New Master Seeds)

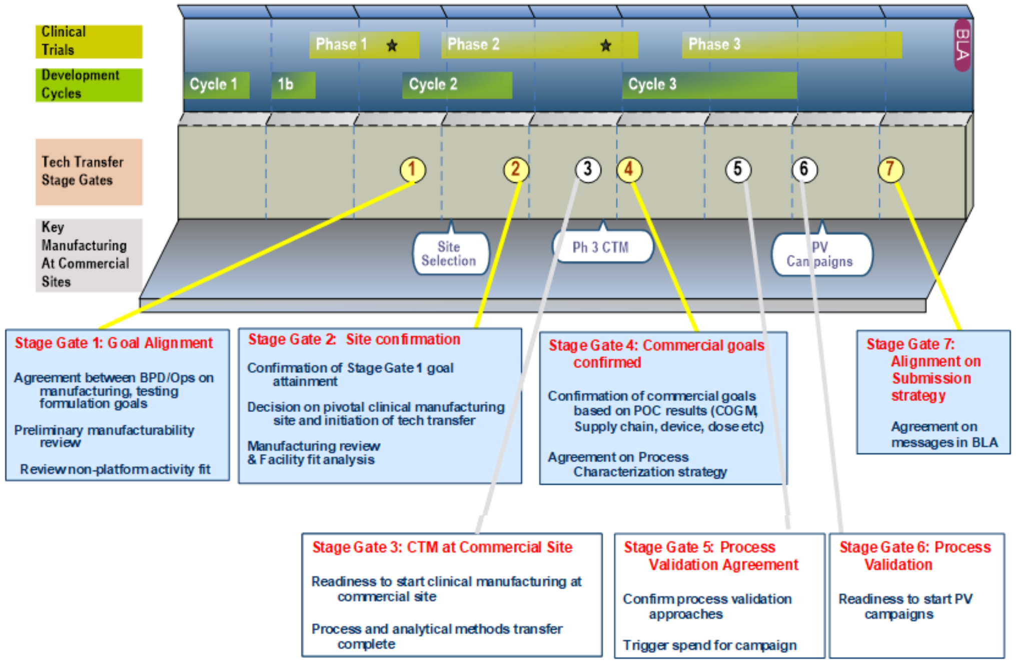
Most vaccines (Live) are prepared from master seeds that LAST FOR THE PRODUCT LIFE SPAN

- Manufacturer's working stock seeds may be manufactured multiple times
- DS bulks may be stored for years

Seasonal vaccines are prepared from master seeds that may CHANGE ANNUALLY to match the vaccine strains with contemporaneous circulating virus

- New product yearly (requires complete lot-release testing)
- New master seeds may be manufactured yearly
- DS bulks may be stored for subsequent year if the strain match is appropriate
- Blending, filling & labeling of DP is based upon conditional release of DS (sterility & potency)

Tech transfer approach, project management, guide



Clinical Trials
Development Cycles
Tech Transfer Stage Gates
Key Manufacturing At Commercial Sites
Phase 1
Phase 2
Phase 3
BLA
Cycle 1
1b
Cycle 2
Cycle 3
1
2
3
4
5
6
7
Site Selection
Ph 3 CTM
PV Campaigns
Stage Gate 1: Goal Alignment
Agreement between BPD/Ops on manufacturing, testing formulation goals
Preliminary manufacturability review
Review non-platform activity fit
Stage Gate 2: Site confirmation
Confirmation of Stage Gate 1 goal attainment
Decision on pivotal clinical manufacturing site and initiation of tech transfer
Manufacturing review & Facility fit analysis
Stage Gate 4: Commercial goals confirmed
Confirmation of commercial goals based on POC results (COGM, Supply chain, device, dose etc)
Agreement on Process Characterization strategy
Stage Gate 7: Alignment on Submission strategy
Agreement on messages in BLA
Stage Gate 3: CTM at Commercial Site
Readiness to start clinical manufacturing at commercial site
Process and analytical methods transfer complete
Stage Gate 5: Process Validation Agreement
Confirm process validation approaches
Trigger spend for campaign
Stage Gate 6: Process Validation
Readiness to start PV campaigns

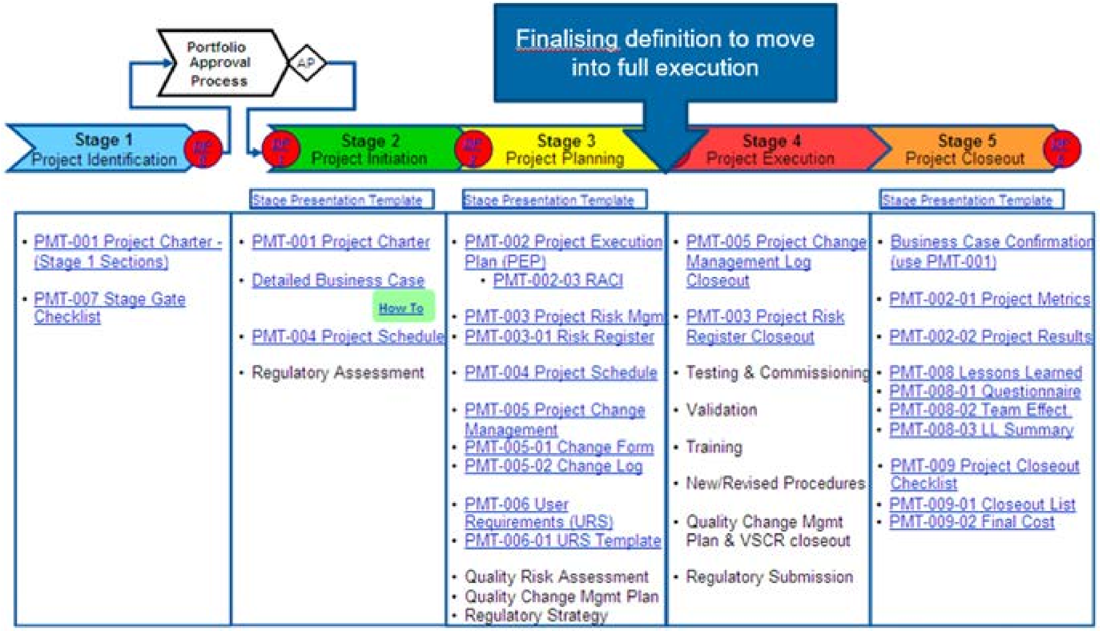
TT Business guide

- Details of the model
- Deliverables
- Governance
- Templates

Category	No.	Deliverable	Key Activities- DS (non-vaccines)	Key Activities- DP	Key Activities-DS Vaccines	Document type and location	Accountable
Strategy	S.3.1	FMC Tech Transfer Plan approved	Update TT and manufacturing schedule. Ensure CMO MSA is in place.	same as DS (non-vaccines)	same as DS (non-vaccines)	Tech Transfer Plan - KIMunity	
	S.3.2	Confirm iPDP and TPP data is consistent with tech transfer plan (number of runs, country specific)	Incorporate any changes in commerical/clinical plan and final configuration into the TT activities	same as DS (non-vaccines)	same as DS (non-vaccines)	Tech Transfer Plan - KIMunity	
	S.3.3	Process risk assessment complete	Update risk assessment for changes during commercial site tech transfer	same as DS (non-vaccines)	same as DS (non-vaccines)	suggest that the output is a risk register spreadsheet rather than a report. That way we can track risks and mitigation over the TT rathering than creating reports (busy work).	
Analytical and QC Testing	A.3.1	Analytical Reference Standard (RS) and Critical Reagent Ownership Transferred to RU	TU to provide sufficient RS material and critical reagent material to RU for cycle 3 engineering runs. TU to produce large RS batch from cycle 3 DS representative engineering runs (for clinical/GMP manufacturing following). RU to take over control of RS	same as DS (non-vaccines)		Memo or system (I'e. LIMS) documenting transfer; Reference Std. Stability Report - Aegis	
Regulatory	R.3.1	NPI complete; risk assessment complete; notify TPN if applicable	Verify NPI and risk assessment are completed			Change Control - Trackwise	QA
	R.3.2	IND submission outline complete and writing initiated (for reporting to clinical product)	Align with strategy identified in strategy meeting			Where are outlines stored?	RA
	R.3.3	BLA submission for new product introduction into licensed facility (submission for existing approved products)	Align with the approved product requirements/expectations			CBE/PAS -Tardis	RA
	R.3.4	Review change control for introduction of product to site and process changes	Ensure alignment with regulatory guidances, regulations and submissions			Combine with R.3.1	RA
	R.3.5	Initiate update of product specification file (PSF)	Update PSF as needed			PSF - Kimunity	QA
	R.3.6	Site master file updated	Verify Site Master File is updated (as required)			SMF - Aegis	QA/RA
	R.3.7	Global Regulatory Strategy Review	Ensure alignment with regulatory and IPDP strategy			Meeting Minutes	RA
	R.3.8	QA SLA or QTA in place for lot release	Verify SLA and QTA are completed			SLA - Aegis, QTA - Legal SAP	QA
	R.3.9	Confirmation of EU readiness (RoW) as required	Ensure compliance with Regulatory Requirements			Audit report in KIMunity	QA
	R.3.10	revise changeover procedure based on NPI assessment and cleaning	Revise changeover procedure based on NPI assessment			SOP - Aegis	QA
Process	P.3.1	Manufacturability Review	Assess fit-to-plant. Produce Facility Fit Reports. Perform Manufacturability Review meetings. Provide tech transfer plan.	Assess fit-to-plant. Produce Facility Fit Reports. Perform Manufacturability Review meetings. Provide tech transfer plan.	same as DS (non-vaccines)	Facility Fit Reports - Aegis; Meeting Minutes - KIMunity	MST
	P.3.2	Process Implementation for Phase 3 Manufacture	Complete site process risk assessment and product introduction documentation (updated if applicable). Identify initial process parameters and in-process controls. Agree upon targets and ranges.	Complete NMF Stage 3 document, or equivalent, and product introduction documentation. Identify initial process parameters and in-process controls. Agree upon targets and ranges.	same as DS (non-vaccines)	Tech Transfer Plan - Aegis; Stage 3 document - Aegis;	BPD/MST
	P.3.3	Phase 3 GMP Run Readiness	Ready site for execution: Test equipment and automation. Receive raw materials including cell bank. Finalize cycle 2 process documentation (MPR/SPR/SOPs; including sampling plan and QC TP), and complete training at mfg site. Define manufacturing support.	Write GMP documentation, including site-specific batch records and master specifications for components and raw materials. Perform training at manufacturing site.	same as DS (non-vaccines)	GMP Documents - Aegis; Training Requirements - eLMS	MST
Facilities and Engineering	F.3.1	Project Execution through Installation and Operational Qualifications (IOQ)	Basis of Design (at ~30% Engineering). Commissioning/Validation Plan with Integrated Commissioning and Qualification (ICQ) scope and resources. Review/update new facility new product introduction plan. Final Design Documents and Construction Drawings.			Capital Project Files	GE
	F.3.2	Equipment Turnover				**Capital Project Files**	**GE**
	F.3.3	Facility PM's and SOP's				PM-SAP; SOP-Aegis	Site Facilities
	F.3.4	Area Release and Environmental Monitoring Performance Qualification (EMPQ), if required				Capital Project Files	GE
Supply Chain	SC.3.1	Clinical & preliminary commercial supply strategy	Generate fill strategy, cold chain/freeze strategy, and logistics. Confirm supply route strategy. Establish import/export plan. Confirm DP storage strategy and identify long term storage locations			?	
	SC.3.2	Clinical forecast review & update as needed	Ensure clinical inventory management at depo, clinical development plan (CDP), maintenance ordering			?	
	SC.3.3	SAP updated	Identify changes, BOMS, vendors, etc.			?	
Raw Materials / Components	RM.3.1	RM components released for use	Ensure raw material have approved released specs. Raw material risk management strategy determined, including second sourcing strategy. Perform a RM sourcing risk assessment. Complete RM supplier audits. Ensure raw materials are release and qualified.			Raw Materials Specs - Aegis; Audis Reports - Aegis/Trackwise; Raw material certification plan - Aegis	
Validation	V.3.1	Sterile filter validation or justify by risk assessment	Report			Risk Assessment - Aegis/KIMunity	
	V.3.2	Full scale cleaning verification plan in place	Plan developed and in place based on NPI risk assessment			Cleaning Verification Plan - Aegis	
	V.3.3	Equipment & Utility qualification	Reports			Equipment & Utility qualification - Aegis	
	V.3.4	Product specific equipment sterilization process validated	Report				
	V.3.5	Facility/Equipment VMP	TER (Technical Evaluation Report)			VMP - Aegis	
	V.3.6	Final Drug Product Container closure qualification	Not applicable	Complete report (development stability/media fills/product stability/container closure integrity)	Drug Substance/qualification	Validation Report - Aegis	
	V.3.7	Media fills or hold confirmed	As appropriate			GMP Documents - Aegis	

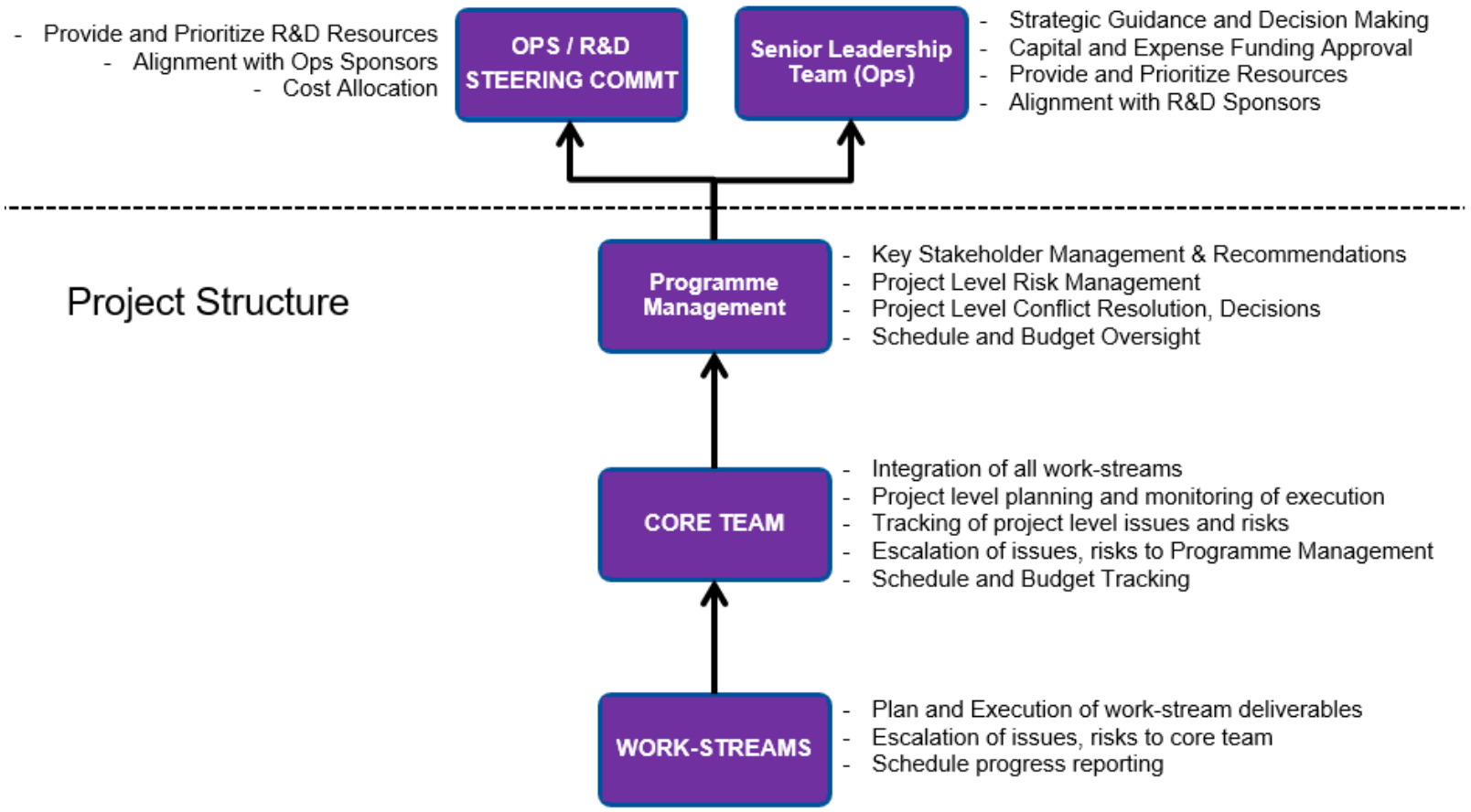
Category

- Strategy
- Analytical and QC Testing
- Regulatory
- Process
- Facilities and Engineering
- Supply Chain
- Raw Materials / Components
- Validation



Portfolio Approval Process
AP
Finalising definition to move into full execution
Stage 1 Project Identification
Stage 2 Project Initiation
Stage 3 Project Planning
Stage 4 Project Execution
Stage 5 Project Closeout
Stage Presentation Template
Stage Presentation Template
Stage Presentation Template
• PMT-001 Project Charter - (Stage 1 Sections)
• PMT-007 Stage Gate Checklist
• PMT-001 Project Charter
• Detailed Business Case
How To
• PMT-004 Project Schedule
• Regulatory Assessment
• PMT-002 Project Execution Plan (PEP)
• PMT-002-03 RACI
• PMT-003 Project Risk Mgmt
• PMT-003-01 Risk Register
• PMT-004 Project Schedule
• PMT-005 Project Change Management
• PMT-005-01 Change Form
• PMT-005-02 Change Log
• PMT-006 User Requirements (URS)
• PMT-006-01 URS Template
• Quality Risk Assessment
• Quality Change Mgmt Plan
• Regulatory Strategy
• PMT-005 Project Change Management Log Closeout
• PMT-003 Project Risk Register Closeout
• Testing & Commissioning
• Validation
• Training
• New/Revised Procedures
• Quality Change Mgmt Plan & VSCR closeout
• Regulatory Submission
• Business Case Confirmation (use PMT-001)
• PMT-002-01 Project Metrics
• PMT-002-02 Project Results
• PMT-008 Lessons Learned
• PMT-008-01 Questionnaire
• PMT-008-02 Team Effect
• PMT-008-03 LL Summary
• PMT-009 Project Closeout Checklist
• PMT-009-01 Closeout List
• PMT-009-02 Final Cost

Governance & structure



Vaccine Development
Building new skills

Stage	Technology	Skills
Strain Research & Development	• Polymerase Chain Reaction (PCR) • Gene cloning & sequencing • Electroporation • Plasmid rescue • Immunogenicity & attenuation • Growth kinetics • Cell culture • Chick-embryo virus cultivation • Growth kinetics • Potency assays	• Molecular biology/cloning • Embryology • Microbiology • Virology • Preclinical development • Process development • Analytical development • Data analysis • Technical writing • Statistics • Biochemistry
Strain Supporting Processes	• Polyclonal antibody production • Micro-neutralisation • Micro-processing • Technical development / remediation	• Cell culture science • Process engineering • QC analytical • Project planning & management • Validation • QA documentation & review • Supply chain, shipping, materials management

Success Factors

Extraordinary interaction & COLLABORATION among operations, R&D, Global Technical Operations, Global Engineering, Reg Affairs, Finance and HR across 5 locations

KEY Activities

- Internal talent identification
- Recruitment
- Temporary training facilities
- Build new BSL2+ labs
- Source new external suppliers and testing labs

Line of sight cross functional strategic learnings

- For Operations
  - Clear view of R&D portfolio
    - Capacity, schedule planning
  - Emerging manufacturing technologies from Development

- For Development
  - Knowledge of plant capacity, capability changes
    - Enables development that fits the plant
  - Operations strategy changes
    - Allows alignment of Development strategy

- For Both functions
  - Early agreement on goals
    - Productivity, COGM, capacity, supply chain etc
    - Development with “End in mind”

Conclusions

- Agile & RFT technology transfer of an ever changing product within tight timelines
- Optimised manufacturing and test processes
  - Collaborate with QA/QC, manufacturing, corporate/trusted partners
- Enable manufacturing through integrated technology strategy
  - Training standards, assay development, technology transfer processes
- Provide technical support to manufacturing and QC
  - Process improvements, validation, microbiology/sterility assurance
  - Complex/non-conformance investigations
- Support product introduction, post launch development, life-cycle management

- Consolidate influenza process activities from US to UK
  - Strain development & manufacture
  - Analytical & Process Development
  - Business processes (e.g. strain selection, regulatory support)
  - Broadened and diversified UK site capability

Application to other products

Challenge the normal. **Evaluate parallel was of working, rather than traditional approaches to Reduce timelines. Risk lifecycle management**

Look to the future & life cycle management efficiencies. Utilize technology, & digital approaches to tech transfer

Leveraging **key skills and capabilities**

Lessons Learned from tech transfer

- Effective relationships, team work & extraordinary interaction & collaboration across different cross functional groups
- Fully define & realise the scope, to include safety, facility, systems/ways of working
- Map current & future state, with clear roles, responsibilities & expectations
- Ensure that there is an integrated schedule with a common and agreed priority, and that support/facilitation resource requirements are fully understood
- Where it makes sense don’t try to create an exact mirror of originating site but understand the receiving site. So have responsibilities in groups where it makes sense
- Define & train out the tech transfer strategy/approach to the entire team as a pre-requisite
- Cross train to maximise flexibility & ensure not too lean. Include succession planning
- Ensure risk management is maintained throughout the project life cycle
- Open, timely and effective communication – communication strategy

QUESTIONS ?

Confidentiality Notice

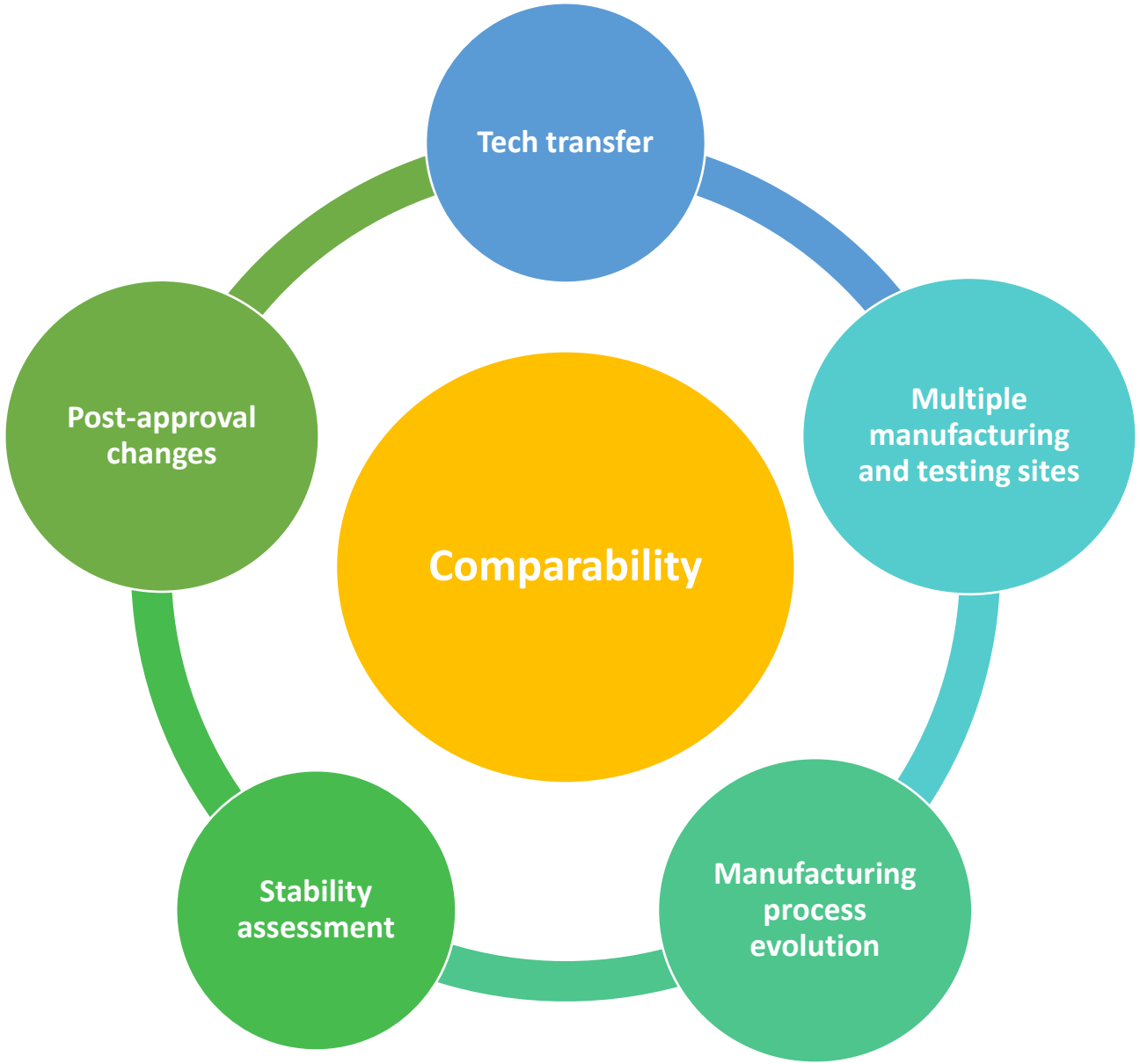
COVAX Workshop- Best Practices for Tech Transfer

Industry Position:

Impact of evolving analytical strategies on comparability, specification and National Control Laboratories testing

Presenter: Cristiana Campa (GSK & Vaccines Europe)

Comparability- why is it so relevant in accelerated scenarios



Comparability is instrumental to manage CMC Challenges for COVID vaccines equitable supply*

- Manufacturing processes for COVID-19 vaccines are moving swiftly
  - Execution of process development with considerably reduced timelines
  - **Evolving knowledge on product, analytics and process**
  - Potential deferral of activities (e.g., optimization/ validation) until after launch to minimize timeline

- To make billions of doses, post-launch supply will likely require:
  - **Use of multiple manufacturing sites** *(& concurrent expansion)*
  - **Need for many post-approval changes**

- For manufacturing changes:
  - Need to **show post-change product is comparable to the pre-change product**
  - Ensure that the pre- and post-change products perform equivalently

** As discussed during COVAX workshop on Comparability, 28 Sept 2020*

Potential Approaches to Demonstration of Comparability for COVID vaccines*

- A risk-based analytical comparability assessment of manufacturing changes, to evaluate a subset of **Critical Quality Attributes** that are **impacted by the proposed changes**
- The use of **release, forced degradation and/or characterization data** to demonstrate comparability
- Key attributes **linked to the pivotal study** in which clinical efficacy has been demonstrated could be used to compare lots
- Where prior knowledge is limited and/ or in the absence of statistically based acceptance criteria, a "clinical development" type approach to comparability may be appropriate, **aimed at demonstrating the preservation of quality attributes without the requirement of process consistency** (in line with ICH Q5E)
- **Global use of general/broader Post- Approval Change Management Protocols (PACMPs)** for routine changes

** Industry (VE/ IFPMA) position discussed during COVAX workshop on Comparability Sept 2020*

Additional Regulatory Advisory Group reflection on analytical strategy for Comparability*

- RAG members stressed that there is a need for **very strong analytical packages and that the analytical package must be focused on the proposed changes in the manufacturing process**. Moreover, it will be important to include stability data and characterization tests in the analytical package.

- In addition to the routine release tests used in a comparability exercise, developers should consider **additional characterization tests** to support comparability over the life-cycle of the vaccine.

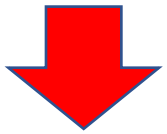
- **If analytical methods are changed during the development of the product, then comparability of the old and new method must be well characterized, or the assessments could prove difficult.** […]

- **As far as possible, the analytical methods should not be modified significantly all along the clinical development phases in order to have a solid baseline for the comparability exercises.** […]"

** Extract from https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines*

What is the meaning of “well- characterized comparability” between methods?

- During development, the analytical procedures used for attributes monitoring may change.
- In the context of COVID-19, such evolution may happen during development and after launch



Implication

- Challenge for Analytical Comparability (i.e., focusing on quality attributes assessment) during development or to support launch/ lifecycle

Possible solution (supporting «well characterized» comparability)

- Use **suitable Reference Standards** to support comparability and analytical bridging
- Focus on **expected analytical methods performances to support method bridging** in case of analytical change for an attribute tested during comparability exercise

Reference Standard Strategy

Uses

- Used as **comparator to verify structural changes associated to process changes** (ICH Q5E)
- **Standard** in analytical procedures (eg for calibration in quantitative tests, reference for identity etc)
- **Control samples** in analytical procedures; **real- time method performance assessment**, with data to supporting continued method performance verification and bridging in case of procedure change.

Lots selection

- During development, reference standard **lots suited/ used for clinical trials** are important to support comparability across different clinical stages – representing the link with the patient.
- In late development, **lots used/ suited for pivotal Phase 3 clinical trials** (establishing safety and efficacy) serve as ideal reference standards for comparability studies **vs PPQ/ commercial lots**
- Lot size need to be large enough to sustain release and NCL transfers; working standard strategy should also be established asap

Suitability requisites

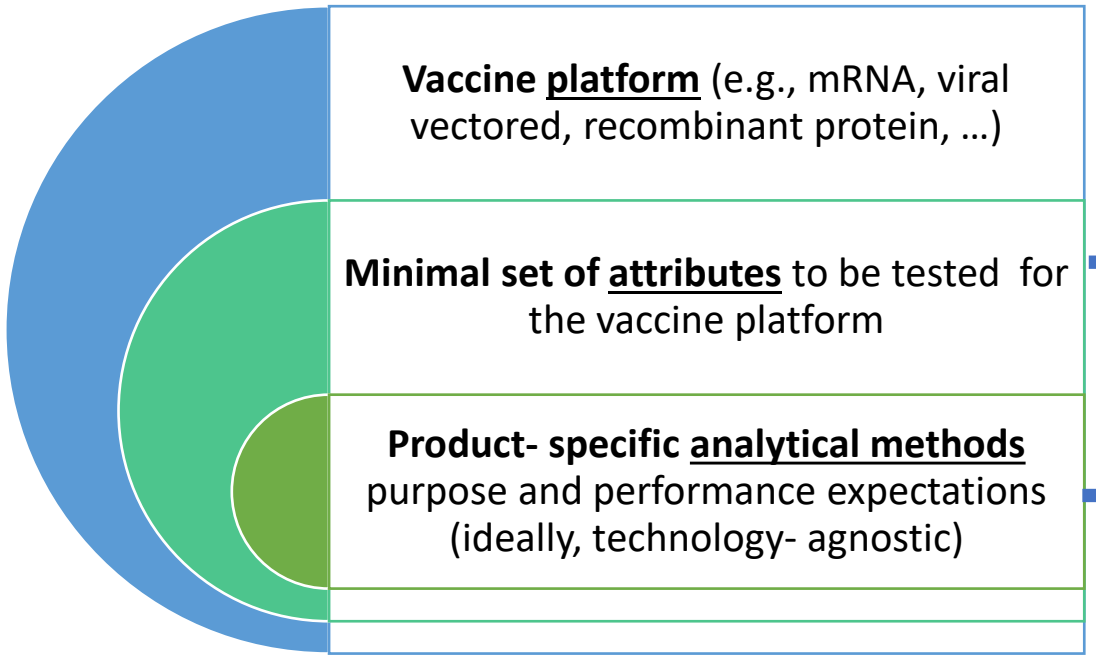
- **Batches representative** of the respective life cycle stage of the product
- **Extensive characterization**
- **Stability** and **storage conditions** defined
- **Qualified** to support use and bridging in case of procedure changes

Support method bridging for comparability- also applicable to other test changes

- ✓ **Identify attributes to be tested** in the specific situation, e.g.
  - for comparability purposes (i.e., attributes impacted by the change)
  - in specifications
  - across different NCLs
- ✓ Clearly articulate the **purpose of the test** (e.g., (i) linked to the change we want to assess in comparability studies, (ii) for specs tests: identity, quantitative content in DP, etc)
- ✓ Focus on **performance expectations** independently on the analytical technology (for product- specific, new assays)

- ➢ Select fit- for purpose analytical methods, minimizing the risk of change
- ➢ Support bridging in case a method change is needed (e.g., innovation introduction, missing technology in a receiving site of a company, different technologies available across different NCLs)
- ➢ Minimize impact of method change on stability predictions/ assessment, as performance expectations would not change
- ➢ Facilitate info transfer from Industry to NCLs and reliance among NCLs

Shift the focus on expected method performances (as opposite to specific tests/ technologies) to support method bridging and NCL mutual recognition establishment



- Publicly disclosed and ideally agreed by Health Authorities globally
- Supporting rapid establishment of analytical strategies for manufacturers and NCLs

(e.g., *Analytical strategy options proposed by EDQM on recombinant viral vectored vaccines for human use*, https://www.edqm.eu/sites/default/files/medias/fichiers/COVID-19/recombinant_viral_vectored_vaccines.pdf or *WHO Evaluation of the quality, safety and efficacy of RNA-based 5 prophylactic vaccines for infectious diseases: regulatory 6 considerations (DRAFT)* https://www.who.int/docs/default-source/biologicals/ecbs/reg-considerations-on-rna-vaccines_1st-draft_pc_tz_22122020.pdf?sfvrsn=c13e1e20_3)

- Based on information and rationales discussed with individual manufacturers (not necessarily publicly disclosed).
- Supporting
    - comparability/ specs testing in case of method changes
    - analytical transfer across different facilities with different technologies
    - alignment/ info transfer/ reliance across NCLs

Regulatory Advisory Group reflection on NCL testing *

- "Several RAG members pointed out the **need for independent testing by National Control Laboratories (NCLs)** due to the fact that COVID-19 vaccines are being developed and manufactured under highly accelerated timelines. […]

- Several RAG members pointed out that NRAs/NRLs should focus on a **minimum set of harmonized critical testing parameters, related to identity, potency and where relevant/appropriate safety based on the product profile**. The batch release tests should to the extent possible avoid in vivo methods, both due to time constraints and accuracy/robustness of the methods. […]

- **Ideally there would be a set of tests recognized globally for each vaccine. However, at present, neither a global mechanism for mutual recognition nor establishing harmonized batch release guidelines are available.**

- The **WHO network of national regulatory authorities (NRAs) and national control laboratories (NCLs)** responsible for testing and release of WHO-prequalified vaccines could potentially facilitate a higher degree of batch release recognition even if the network members have no legally binding obligation to recognize the release results from other network members. […]"

** Extract from https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines*

NCL testing, potential roadblocks for agile supply of vaccines to patients

- Limited responsiveness of Industry and NCLs to innovation and suboptimal (obsolete) analytical strategies, due to constraints imposed by the current emergency (e.g., *in vitro* vs *in vivo* testing; rapid micro methods (RMMs) as a replacement for compendial micro methods)

- Multiple NCL testing labs, several transfers from Industry to NCLs (time and supply risks increasing with number of NCLs)

- High testing demand for NCLs, potential bottleneck **for COVID-19 and other vaccines** supply- how many lots to be tested?

What can be done NOW to accelerate NCLs testing and prevent roadblocks in the next months/ years?

- Several initatives are ongoing to improve alignment and recognition between NCLs (e.g., WHO, OCABR) *

- As reported above, shift the focus on expected tests and method performances (as opposite to specific tests/ technologies) to support Industry/ NCLs methods transfer, fast innovation introduction and NCL mutual recognition establishment

- Use platform knowledge more extensively to support definition of analytical strategies, method change management and support testing readiness (industry and NCLs)

- **Foster NCLs/ Industry collaboration**, also helping establishment of harmonized criteria for definition of the number of lots to be tested by NCLs, considering, for instance:
  - timely and structured review of company data on all manufactured lots
  - analytical method knowledge/ shared expertise between companies and (selected) NCL(s)
  - information and material exchange regarding reference standard and reagents
  - time from launch and quality control trends assessment

**More detail at*

- *https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines*
- *https://extranet.who.int/pqweb/sites/default/files/documents/WHO_OperationalTool_EfficientLotRelease_v20Jan2021.pdf*

Assay tech transfer – points to consider

- Relevance of **existing cross- company, cross- agency/NCLs network** to support introduction of innovative, high performing tests (e.g., Vac2Vac or Next Generation Sequencing initiatives)

- Importance of **timely interaction of Companies with reference NCL(s)** to facilitate readiness for testing and results comparison

- **NCL recognition of some of the results from companies** → NCL focusing on selected key tests, with risk- based approach

- Use of platformization of methods across projects (for a given vaccine type) → faster readiness in NCLs & faster development and validation within the companies

- Importance of visibility from Industry on NCLs progress on assay development, for an effective support/ partnership

Illustrative Example of collaboration between Industry and NCLs

- ELISA for potency testing of a vaccine, co-development between AGES/ BASG and GSK
- *In vivo* testing with very long lead time (more than 1 month), also executed at the OMCL
- Common need to switch to an *in vitro* approach → collaboration cross industry-NCL to set a method:
  - Characterization of antibodies originating from AGES/BASG and GSK, including specificity in the presence of aluminum adjuvant.
  - Co-selection of the most suitable antibody (*Ph. Eur. general chapter 5.2.14*)
  - Development of immunoassay including forced degradation studies, definition of optimal GMP settings and optimization of protocol
  - Immunoassay qualification/validation including parallel testing of immunoassay and challenge test and testing of altered samples- done at both AGES/BASG and GSK

Example of Collaboration between Industry and NCLs- importance of the reagents

- Learnings from co-development between AGES/BASG and GSK
  - Importance of trainings in both labs
  - GEMBAs among scientists and managers (on site as possible) was also ensured
  - Don’t forget about legal agreements (CDA and MTA) – possibly execute this kind of studies in the frame of collaboration initiatives (eg Vac2Vac)

Key takeaways

- In the context of COVID-19 emergency, analytical method changes could take place either due to company needs (e.g., evolving knowledge, cross- testing site transfers/ changes) or considering transfer to National Control Laboratories (NCLs).

- Wherever possible, practice **cross- recognition of NCLs**

- Some proposals are made to support the evolving of analytical strategies for COVID-19 vaccines, with risk- based approaches, ensuring reliable Comparability, Specification testing and NCL release:

  - Reference Standard strategy
  - Definition of minimum set of tests (platform- specific) and analytical method purpose and performance expectations (product- specific)
  - NCLs/ Industry collaboration

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Questions?

Regulatory perspective: NRA and WHO EUL/PQ

SWAT manufacturers workshop

“Best practices for tech transfer”

Carmen Rodriguez Team lead vaccines Prequalification

Department of Regulation and Prequalification (RPQ)

27 January 2021

World Health Organization

Goal & objectives

Goal of this WHO work: to optimize access & availability to safe, efficacious, quality-assured COVID-19 products by further aligning regulatory processes

Objectives of today's presentation:

- Provide an overview of WHO assessment processes of vaccines under technology transfer

WHO EUL/PQ submission requirements for evaluation of COVID-19 candidates & areas of specific guidance (examples)

Areas of COVID-19 specific guidance

Non-clinical & Clinical assessment

- Non-clinical information
- Clinical development programme
- Ethics Committee approval of clinical trials
- Evidence of GLP/ GCP conduct
- Evidence for registration
- Clinical trial design
- Statistical Considerations
- Clinical trial end-point assays
- Vaccine lots used in clinical studies and lot-to-lot consistency studies
- Subject exposure to a new vaccine in trial
- Follow-up in clinical trials
- Requirement for a risk management plan
- Specific data:
  - Clinical efficacy data
  - Immunogenicity data
  - Duration of protection
  - Indirect effect
  - Target populations
  - Safety data
  - Benefit risk assessment report

Manufacturing, QC & labelling

- Characterization of cell banks
- Characterization of master and working seeds
- Process validation (based on risk assessment, incl. production lot consistency & post-listing commitments)
- Justified specifications
- Stability data
- GMP inspection reports
- Process change
- Labelling

WHO's assessment decision will be guided intra alia by **status of clinical development**, extent of the **available quality, safety and efficacy data,** evidence of **compliance, process validation** and reference NRA **regulatory approvals**

Source: https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO_Evaluation_Covid_Vaccine.pdf

Source of candidate vaccines

Initial development

SRA, Functional NRAs

Technology transfer

India,
Japan, South Korea,
South Africa
Argentina&Mexico

Fillers

Assessment on what data may be required

Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process

	Manufacturer	Name of Vaccine	NRA of Record	Platform	EOI accepted	Pre-submission meeting held	Dossier accepted for review*	Status of assessment**	Anticipated decision date***
1.	Pfizer BIONTECH	BNT162b2/COMIRNATY Tozinameran (INN)	EMA	Nucleoside modified mNRA	✓	✓	✓	Finalized	31/12/20
2.	AstraZeneca	AZD1222	Core – EMA Non-COVAX	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	✓	✓	✓	In progress Core data Non-Covax. Covax data to be reviewed as EMA post approval change	Earliest by EMA End of January (non-Covax) Additional nodes in March/ April for Covax
3.	SK BIO AstraZeneca	AZD1222	MFDS KOREA	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	✓	✓	18 Jan Additional data expected on 29 Jan 2021 (CMC for SK Bio)	Core data (non-covax) in progress (in parallel with EMA). SK Bio data assessed in conjunction with MFDS	Earliest 2nd half Feb 2021
4.	Serum Institute of India	Covishield (ChAdOx1_nCoV-19)	DCGI	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	✓	✓	✓	In progress	Mid Feb 2021
5.	Sinopharm / BIBP[1]	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	NMPA	Inactivated, produced in Vero cells	✓	✓	✓	In progress	Earliest March
6.	sinovac	SARS-CoV-2 Vaccine (Vero Cell), Inactivated	NMPA	Inactivated, produced in Vero cells	✓	✓	Data submitted on 13 January 2021 for inspection purposes. Dossier expected end January.		Earliest March
7.	moderna	mRNA-1273	EMA	mNRA-based vaccine encapsulated in lipid nanoparticle (LNP)	✓	✓	Expected in February		Estimated end of Feb 2021
8.	janssen Infectious Diseases & Vaccines	Ad26.COV2.S	EMA	Recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine			Rolling data to EMA – Dec, Feb, April (critical	Not yet started. Use abridged	Earliest May – June 2021

https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_25Jan2021.pdf

Technology transfer options

Transfer of starting materials (including cell banks and seeds), manufacturing process and analytical methods

Different company	Same company - different sites/CMOs
demonstration of analytical comparability at comercial scale (PPQ batches)	Comparability of commercial scale batches with clinical batches to demonstrate safety and efficacy
	PPQs of different sites

Regulatory

Evidence that product manufactured in different sites following technology transfer is equivalent to the batches used to demonstrate safety and efficacy.

Authorization for emergency use by relevant authorities (NRA of record) prior to EUL decision.

WHO EUL

World Health Organization

Assessment performed in collaboration with relevant authorities (different models)

WHO EUL conditions and commitments:

Post-authorization monitoring critical: Changes, monitoring performance (programmatic, efficacy/effectiveness and safety of the vaccine

Think out of the box, Unite, Collaborate & Cooperate

- Global cooperation and coordination on regulation.
- Facilitation of authorization of Covid-19 at global level.
- Mechanisms for review of data for emergency authorization and facilitation in other countries.
- Mechanisms to monitor performance of the vaccine (quality, safety and efficacy and programmatic) and collaboration between member states.

World Health Organization

WHO/Otto B.

WORKING TOGETHER

Department of Regulation and Prequalification, WHO

Thank you