Developing Vaccines at Pandemic Speed

WCBP

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Agenda

- Approach to Rapid Response
  - Product and Process Development
  - Analytics
  - Clinical Manufacture
  - Regulatory Approaches
- Case Study – Ebola
- Case Study – COVID
- Lessons Learned and Future Opportunities

How do we develop vaccines with speed to address a pandemic?

Key Focus Areas:

- ❑ Product and Process Development
- ❑ Analytics
- ❑ Clinical Manufacture
- ❑ Regulatory Interactions and Filing Approaches

Typical Timeline for Vaccine Development

This timeline is not acceptable for an epidemic or pandemic!

Rapid Product and Process Development

What product technology will be used?

- mRNA - Can develop with speed but unclear the duration of memory response thereby requiring periodic boosts
  - Challenge to generate sufficient supply for a global market
- Viral Vectors – variable memory response across the spectrum of viruses
  - ERVEBO – single dose regimen with memory response
  - J&J Zabdeno® /Mvabea® - requires a two –dose regimen
- Protein based vaccines - variable protection
- NO PERFECT SOLUTION…….

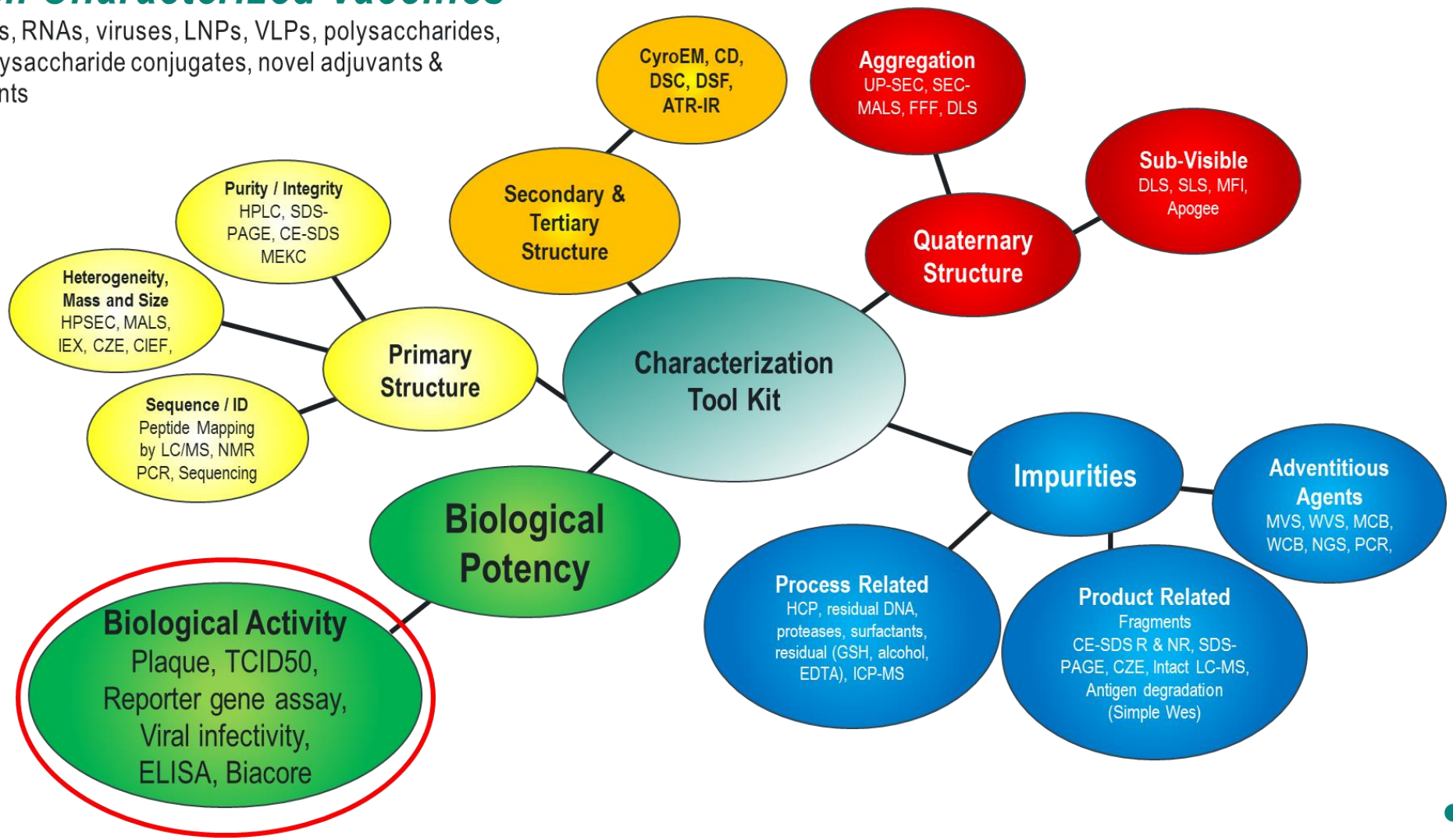
Platform Approaches

- Companies leverage their existing platform processes in order to gain speed
  - Strong technical knowledge of the platform – process and analytical
  - Leverage existing pre-clinical toxicology studies
  - Existing materials/consumables allows work to begin immediately
  - Stays aligned to existing manufacturing platforms allowing quick transitions to GMP manufacturing
  - Single Use technologies and standardized unit operations allows for rapid transfer to commercial facility
  - Implement continuous manufacturing processes to addresses product demand

Analytics

"Well Characterized Vaccines"

Proteins, RNAs, viruses, LNPs, VLPs, polysaccharides, and polysaccharide conjugates, novel adjuvants & excipients



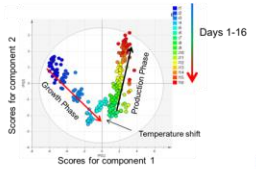
Transition toward Real Time Release

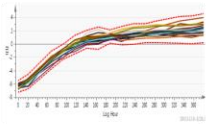
Conventional QC/QA

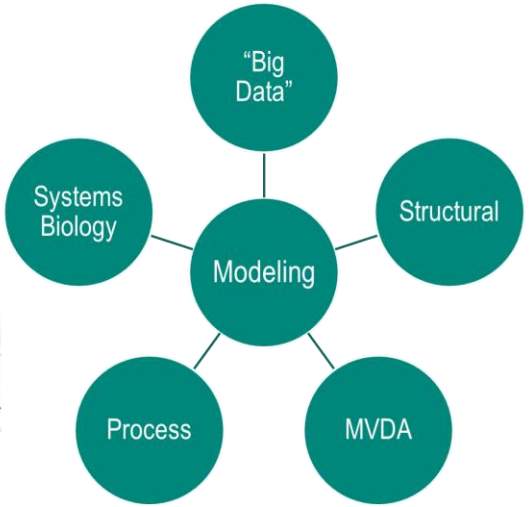
- Incoming QA/ Manufacturing
- Sampling
- Chain of Custody
- QC Testing
- Electronic Systems
- Data for Decision

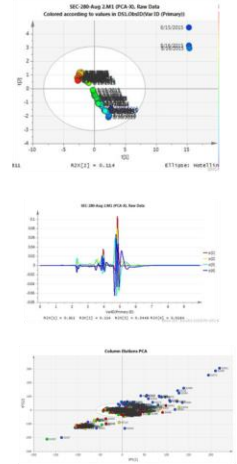
Future: Real Time Quality Release

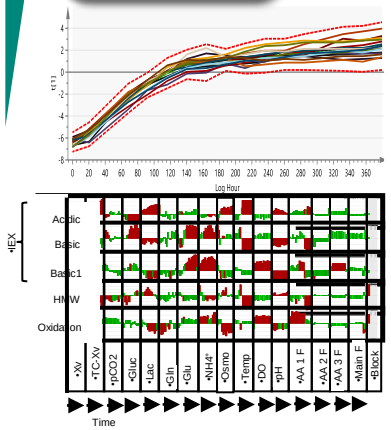
- Shop Floor Insitu QC testing
- Electronic Systems
- Data for Decision



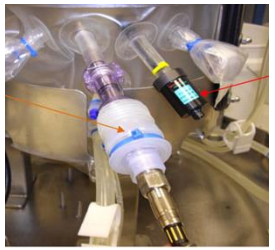








Predictive Product Attribute Control



Immediate verification of Product/ Process Attributes

Thermo Q-Exactive LC-MS

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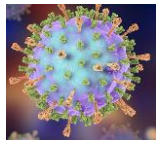
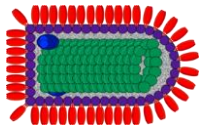
End to End Analytics for Multi-Modal Vaccines

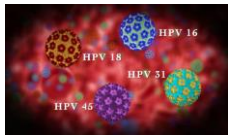
- Live attenuated viruses
- Genetically modified viruses
- Virus-like particles (VLP)
- Ps-conjugates
- mRNA vaccines



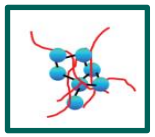
Live viruses



Ebola vaccine rVSV-ZEBOV



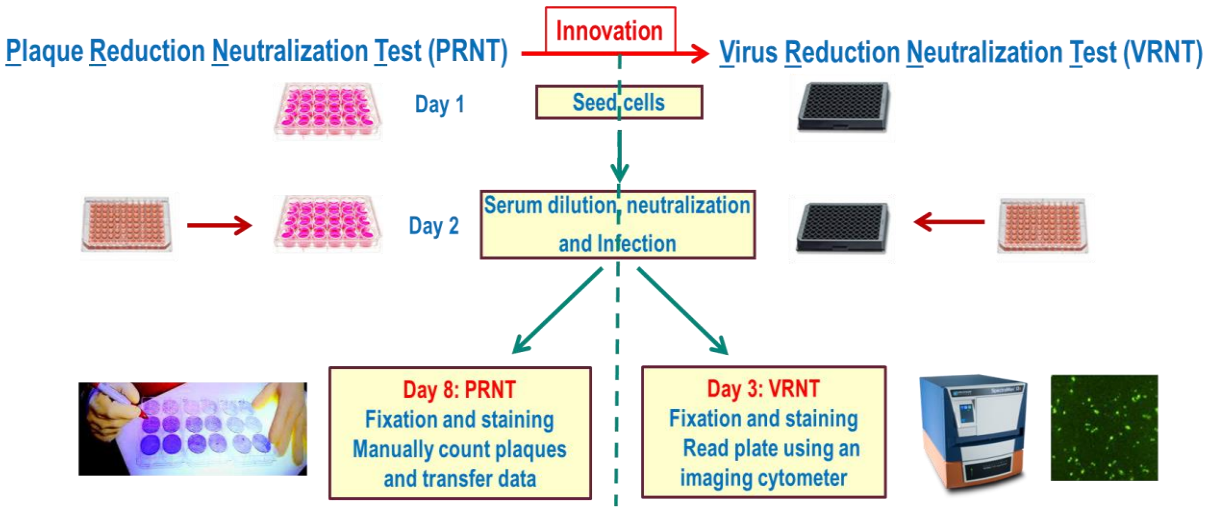
Gardasil (VLP)



Ps-CRM conjugate

Attribute	Analytical Methods
Identity	Sanger Sequencing, Immuno-plaque
Potency	Plaque, qPCR, reporter gene assay, cell based ELISA
Residuals	PCR, qPCR, spectroscopy
Safety	Sterility, Endotoxin, Mycoplasma, Adventitious agents

- Innovation in vaccine clinical assays
- Scientific impact:
  - 1 patent
  - 2 publications
- Business impact:
  - Faster turn-around time
  - Higher throughput
  - Lower cost



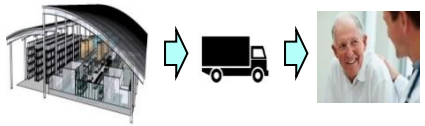
Clinical Manufacture

- Self supporting manufacturing facility – media/buffer manufacture, sterile supply
  - Minimizes potential supply chain concerns
- Platform processes
  - Ability to manufacture different platforms (mRNA, viral vectors and bacterial vectors)
  - Provides ability to purchase and stock raw materials (powder medias and salts) and consumables
  - Maintain key process equipment
  - Staff trained in process operations allows for rapid response
  - Risk based approach to manufacturing schedule

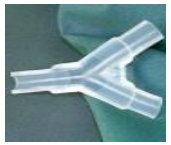
- Clinical Facility
  - Flexible facility – able to do non-GMP and GMP work
    - Development work can continue while manufacturing clinical materials
  - Combination of Single Use and Stainless steel to support multiple platforms
  - Open floor concept to support multiple unit operations

Flexible Manufacturing Facilities of the Future

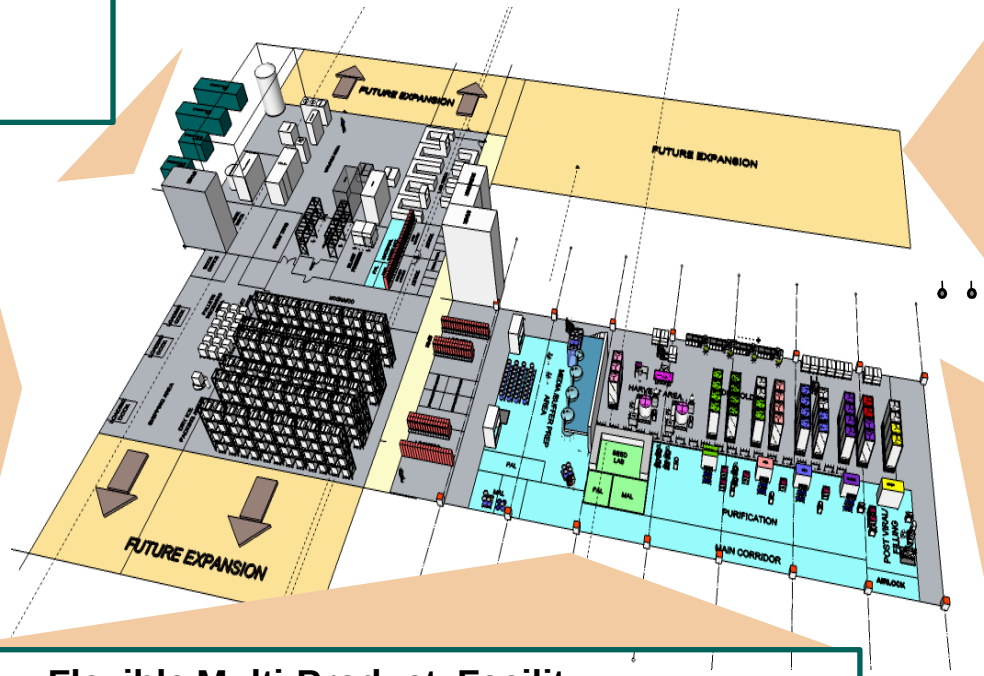
Synchronized supply chain



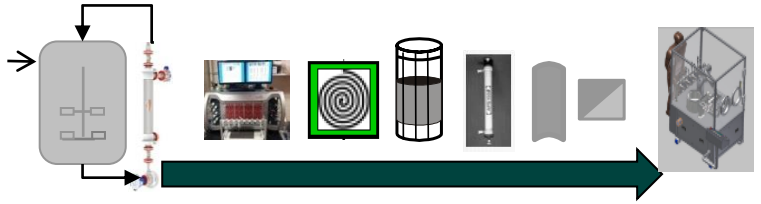
Single Use Closed Processing



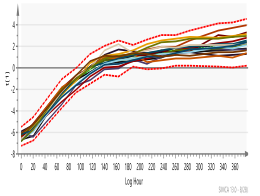
Molded parts



Automated Continuous Processing

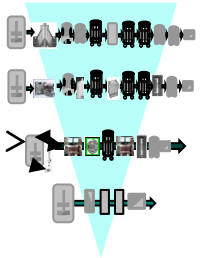


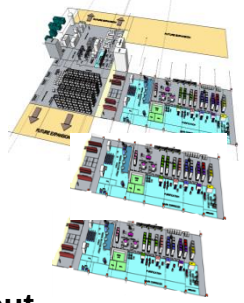
Adaptive Process Control via PAT Tools and Models



Flexible Multi-Product Facility

Modular/Podular Concept





Expansion via Scale out

Regulatory Approaches

- With no adequate approved alternatives available to diagnose, treat or prevent a life-threatening disease
- Enhanced interactions and early dialogue with the agencies throughout development to rapidly get product to the patient.
  - Communicating program intent to FDA and scheduling periodic meetings.
  - Providing key clinical data to support product safety to proceed rapidly into Phase 2 and 3 trials.
  - Partnering with the FDA on expected timelines associated to the EUAL filing submission

For Ebola:

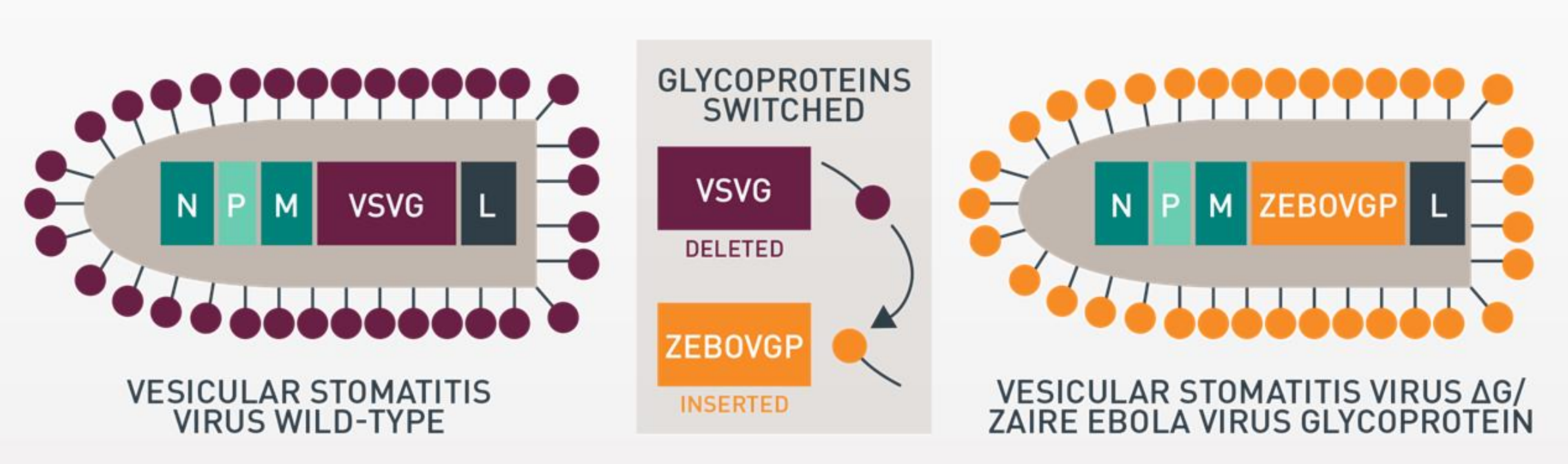
- From 2015-2019, there were 23 informal and formal regulatory CMC interactions.
- Filed EUAL May 30, 2016 however it was not enacted
- Doses were provided under a Pre-License Patient Access clinical protocol

ERVEBO Case Study

CASE STUDY: ERVEBO® (V920 Vaccine)

ERVEBO
(Ebola Zaire Vaccine, Live)

rVSVΔG-ZEBOV-GP, live attenuated



This vaccine is a live, attenuated, recombinant vesicular stomatitis virus (rVSV)-based, chimeric-vector vaccine, for which the VSV envelope protein was deleted and replaced (ΔG) by inserting the envelope glycoprotein (GP) of Zaire ebolavirus (ZEBOV). There is no live Zaire ebolavirus in the vaccine.

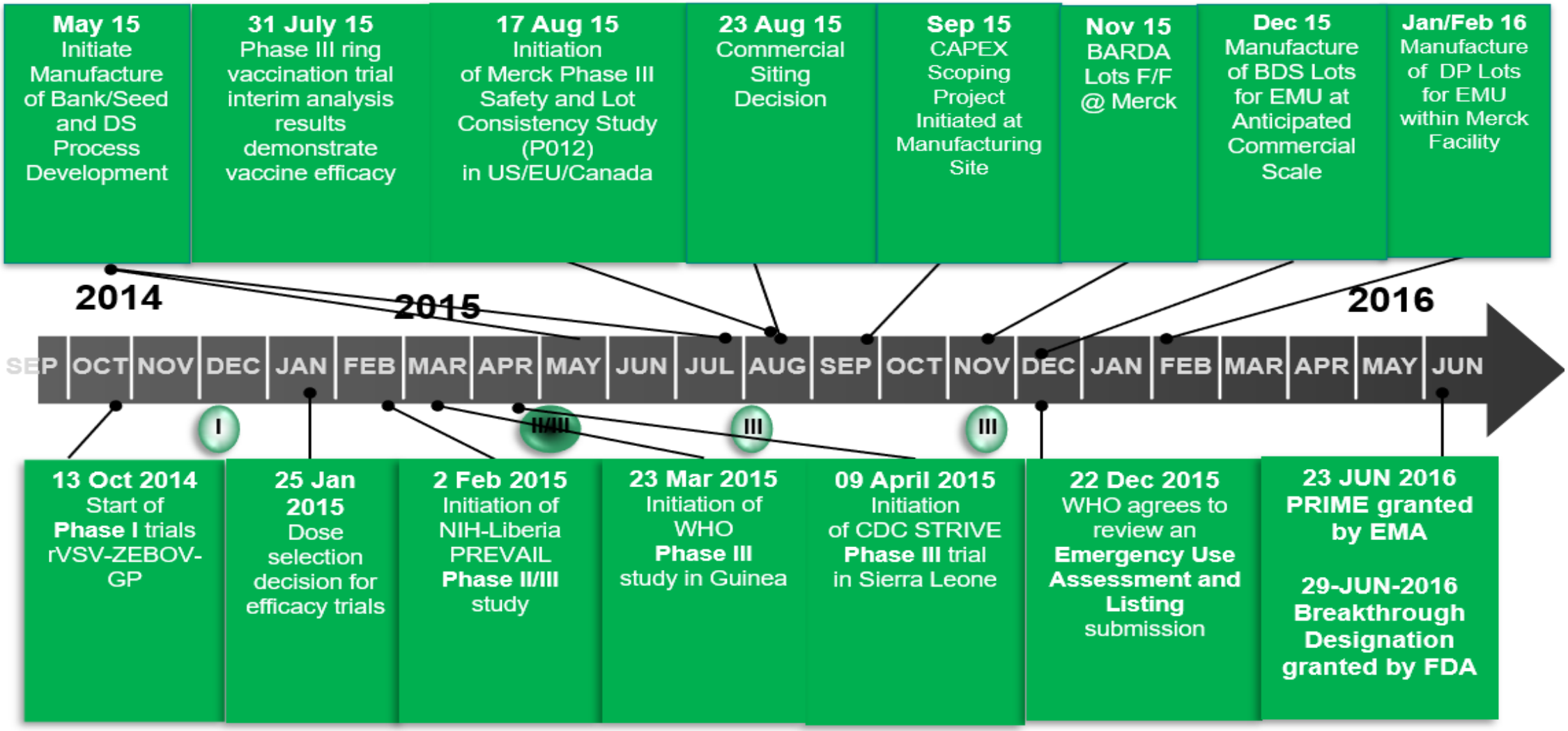
Merck's Approach to Address Potential Vaccine Needs and Vaccine Availability

- **Collaborate with current dose owners and stakeholders to align on best use of existing doses of vaccine (~150 – 170K)**
  - Intended for expanded ring vaccination trials, new or expanded trials for at-risk US-based and ex-US populations, etc.

- **Ramp up Merck Clinical manufacturing capabilities to produce additional doses that could be deployed in the case of expanded or new outbreak**
  - Ethical obligation to ensure vaccine available
  - Utilize the WHO Emergency Use Authorization process (new process/first time application)

- **Move monovalent frozen product forward for licensure as efficiently as possible**
  - Produce required safety database and demonstrate evidence of clinical benefit.
  - Prepare commercial manufacturing facility and execute on process transfer and PPQ activities.

Merck's Vaccine Milestones and Accelerated Development Timeline



Clinical Manufacture - Approach to Accelerate

Development Focus

-Scale-up to 400 Roller Bottle scale (~4.5X increase from clinical batch size)

Parameters

-Multiplicity of Infection
-Plant density
-Day of Infection
-Harvest Time
-Depth Filtration
-Enzyme Reaction
-TFF

End to End – 1 year

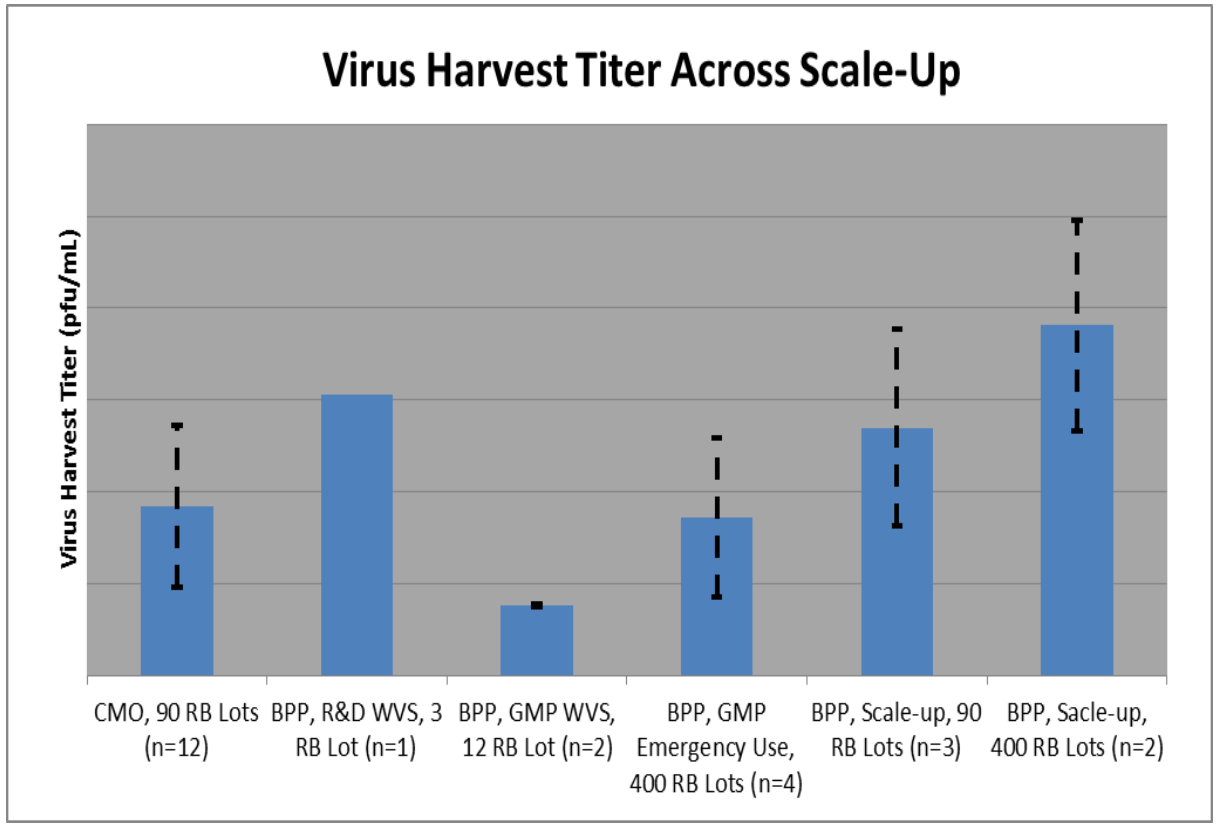
- Produced Drug Substance sufficient to make >750k doses
- Produced >125k doses (10-Dose image)
- Emergency Use Assessment & Listing (EUAL) filed 30May2016
- Doses available for use – 30Sep2016

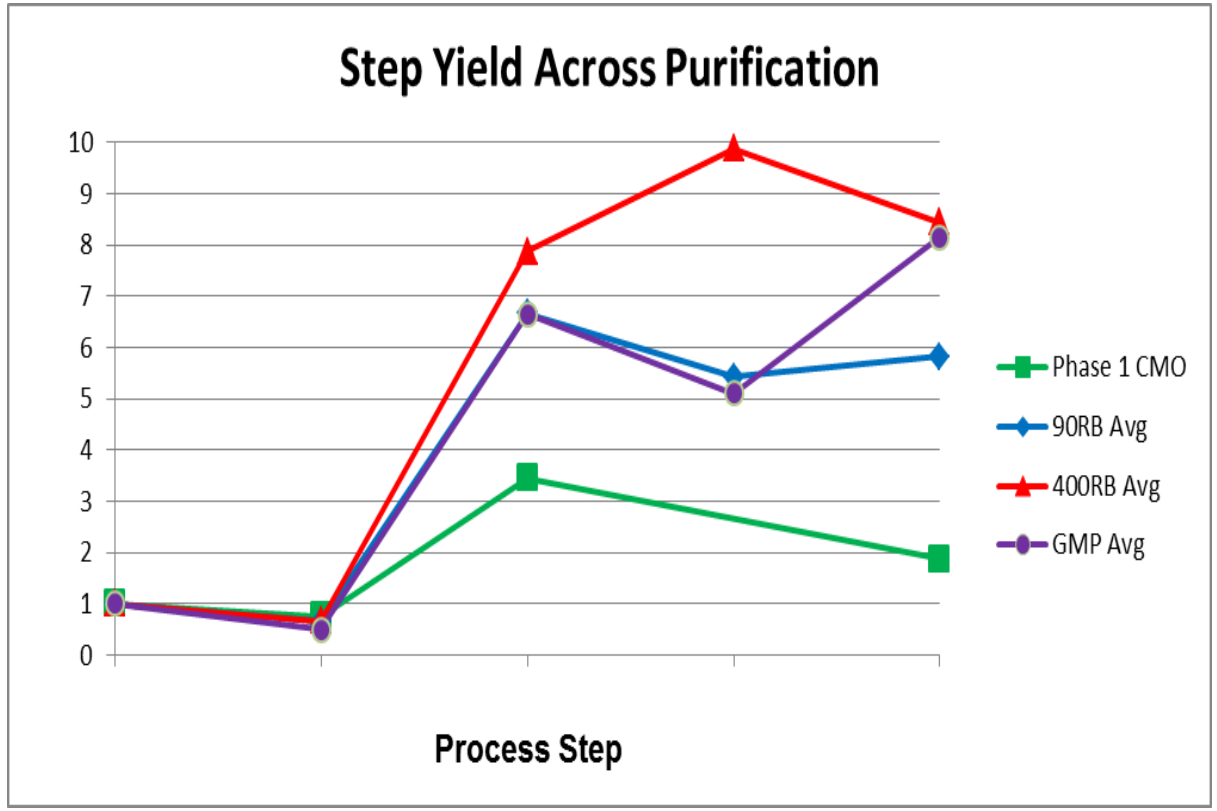
Approach

-Leverage prior knowledge of cell line and roller bottle process operations

Process Development – Scale Up

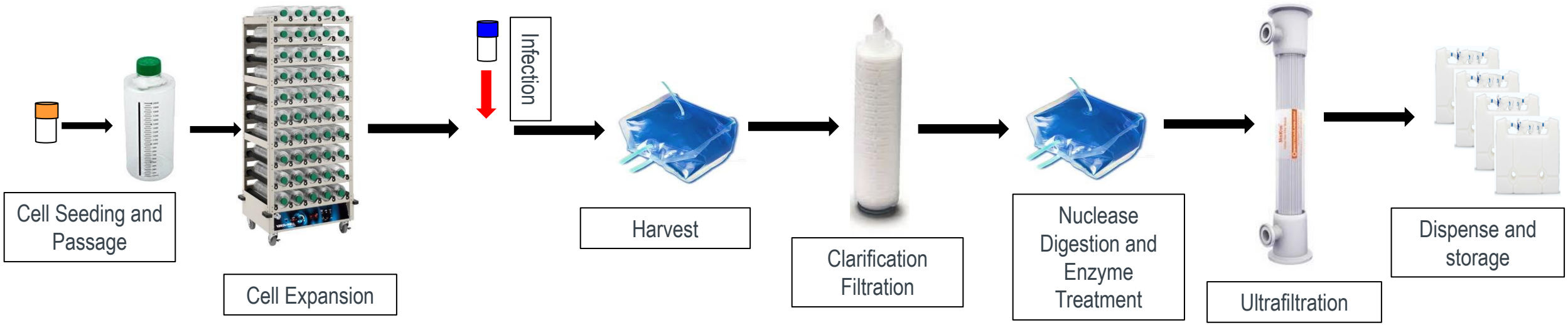
Scale-up at Merck is comparable to CMO and clinical experience.
Improvement in overall purification recovery was achieved.





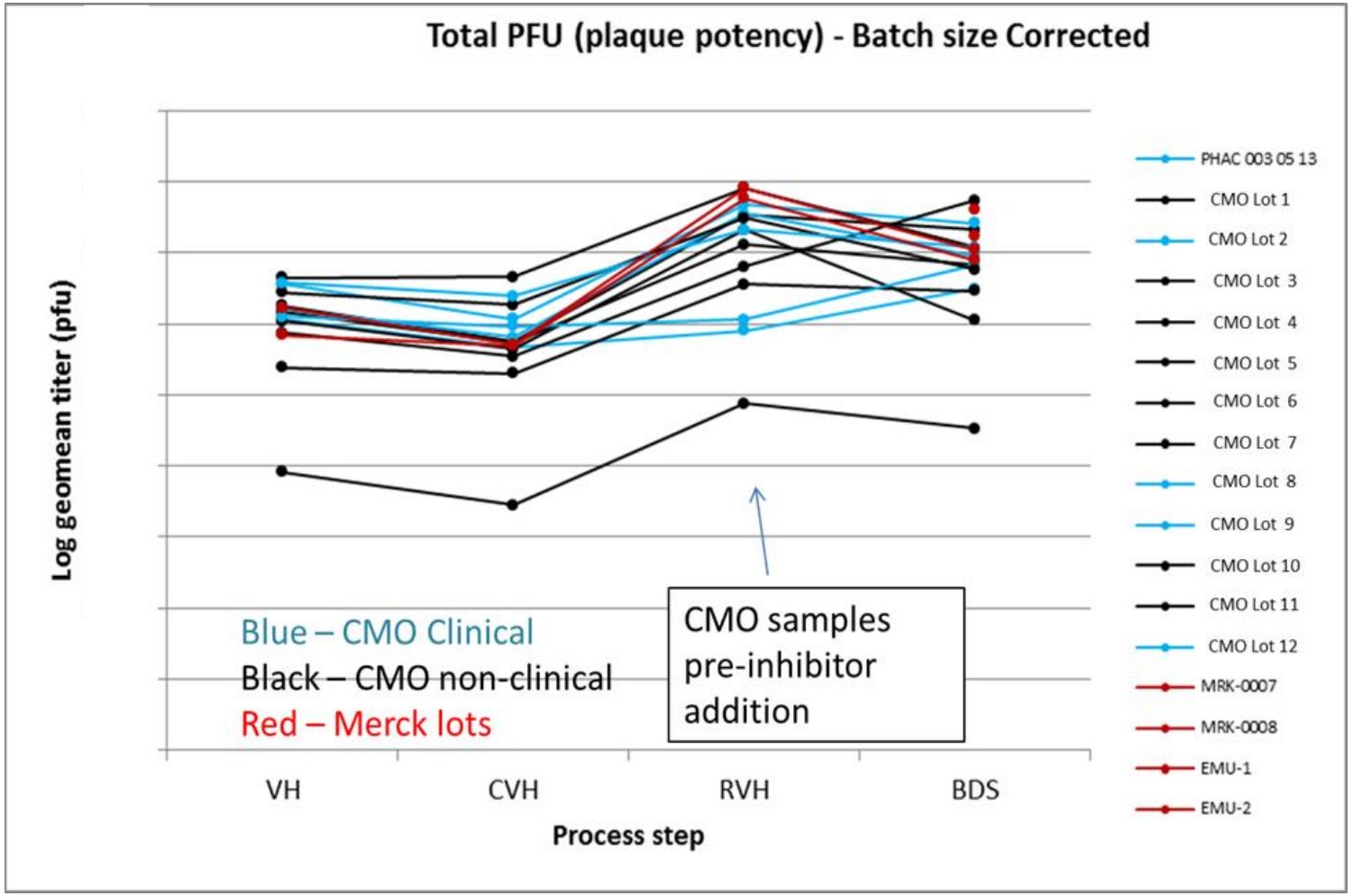
ERVEBO ® Drug Substance Process

ERVEBO® Ph 3 Process



Single Use fully closed process

Comparison of Merck Commercial DS Process to Clinical Process



Product potency across the process is consistent across all scales from lab to commercial scale and aligns to CMO experience.

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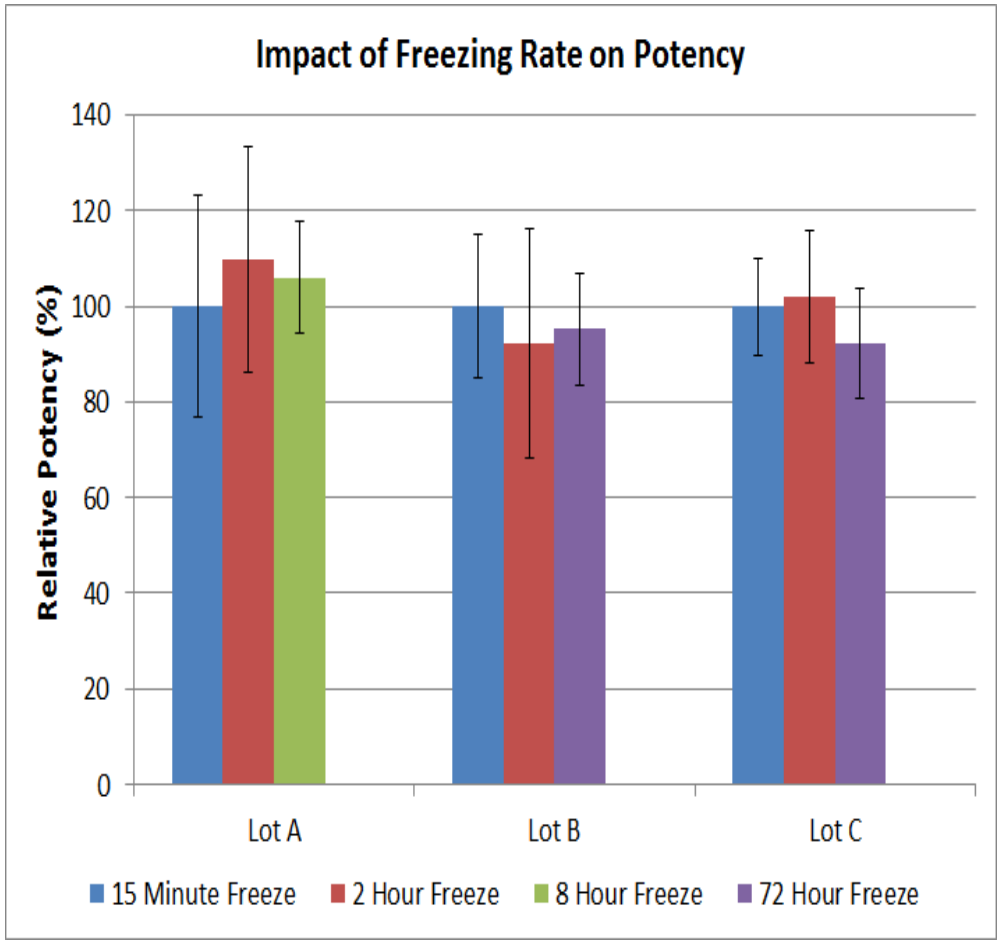
DP Process Development

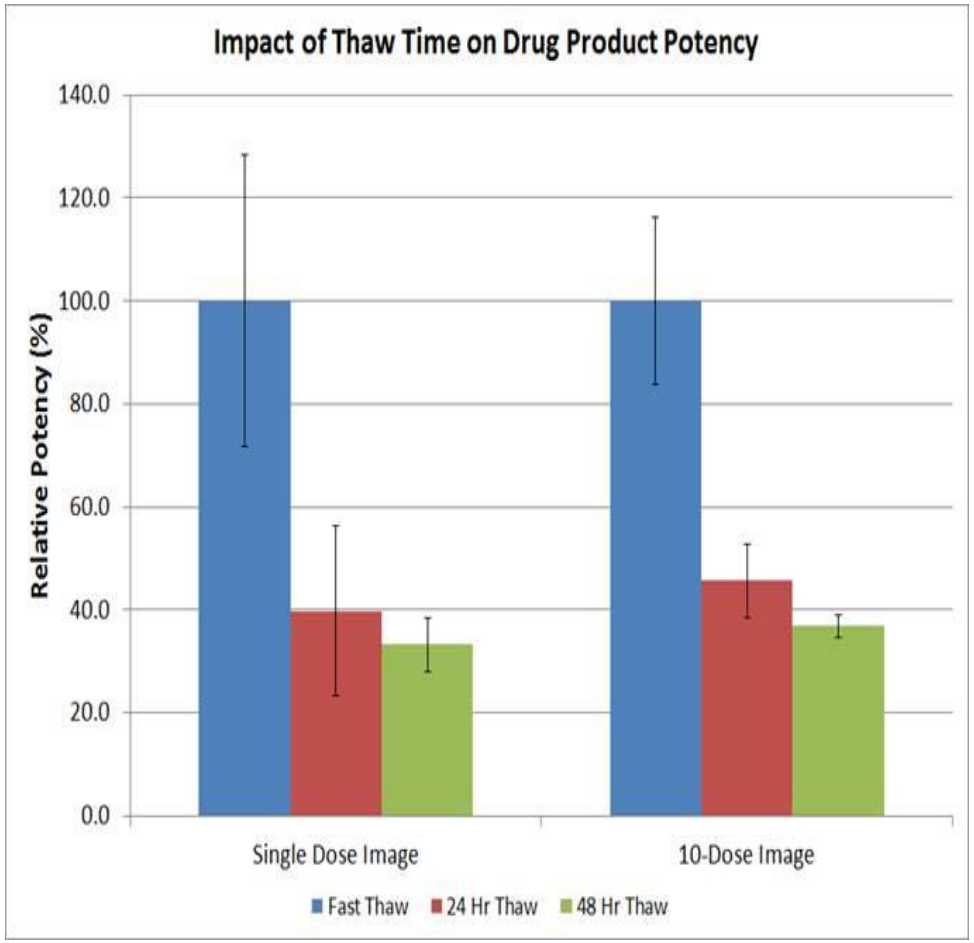
- Impact of shear and mixing on final formulated bulk (FFB) – no impact (data not shown)
- Impact of DP freezing and thawing
- DS dilutability studies to target a final DP potency (linear, data not shown)
- Short-term stability studies to investigate the impact of normal manufacturing times and temperatures on drug product potency
  - Establish 2-8C storage
  - Understand Time Out of Refrigeration (TOR)

DP Freeze Thaw Studies

Method of freezing does not appear to impact potency



Thaw product at RT to minimize the thaw time.



Multiple freez thaw has no impact on stability (data nnot shown).

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ERVEBO® Drug Product Profile

- **Single dose and 10 dose image**
  - Provides flexibility on treatment approaches
- **Stored at -70C**
- **Short term storage 2-8C for 4 weeks for use in the field**

Approach to Analytical Comparability

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

1) Show Comparability
2) Set prospective criteria for formal commercial comparability

1. Contract Manufacturing

- Initial Clinical Dose experience

2. Biologics Pilot Plant

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

3. Commercial

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

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

ERVEBO Emergency Use Manufacture Summary

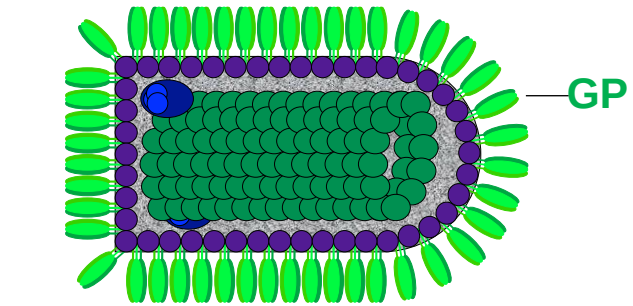
End to End – 1 year!

- ❑ Single Use Technology to support rapid transfer to commercial facility
- ❑ EUAL Vaccine for Ebola was filed May 30, 2016
- ❑ Available for Use – September 30, 2016
- ❑ Supported outbreaks from 2016 – 2020
- ❑ ERVEBO ® Approved – USA – Dec 19, 2019, EU- Feb 14, 2020

COVID Vaccine Case Study

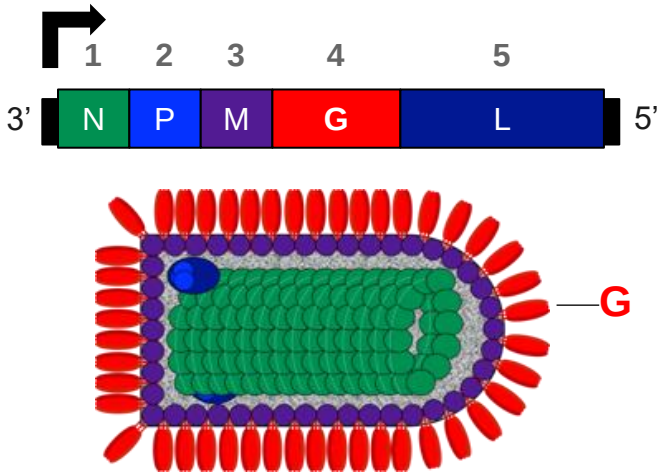
Merck-IAVI: Employ VSVΔG Chimeric Virus Platform Used for ERVEBO®

VSV = vesicular stomatitis virus



ERVEBO

VSV (Indiana) RNA genome



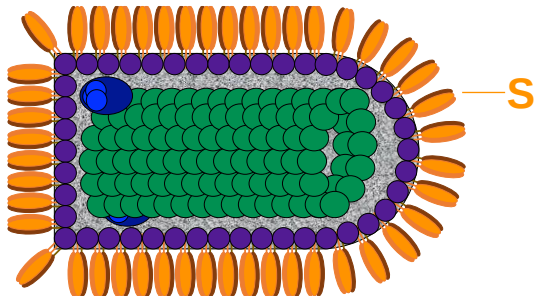
Delete VSV G gene (ΔG)

Substitute gene for heterologous viral glycoprotein

VSVΔG-ZEBOV-GP

Replication-competent chimeric viruses

VSVΔG-SARS-CoV-2

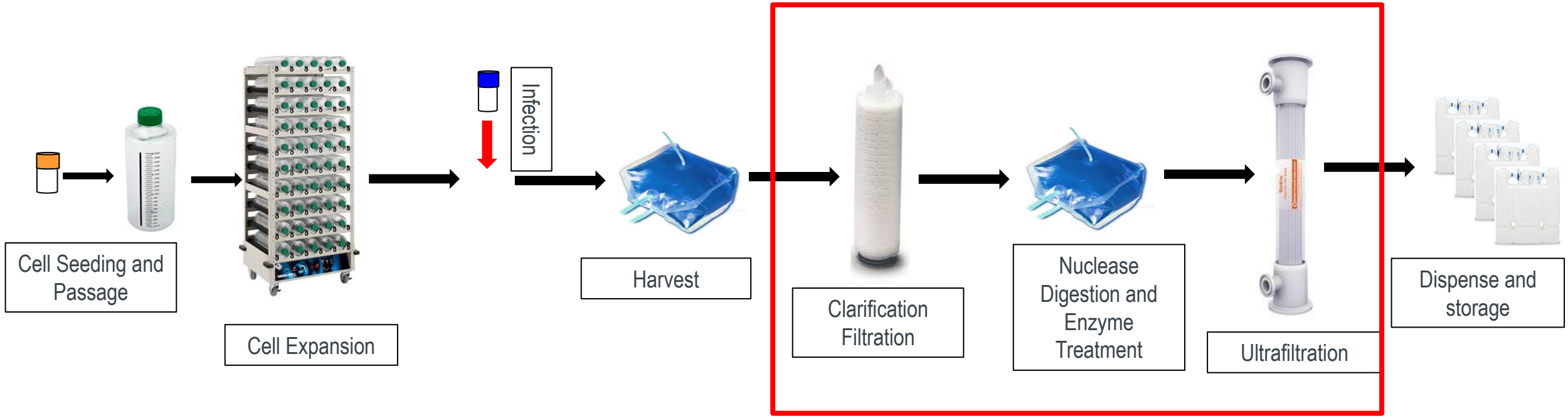


CHALLENGES

- VSV and CoV are from different virus families
- VSV and CoV replication cycles vary considerably
- The two viruses replicate in different cellular compartments
- VSV G and CoV S concentrate in different regions of the cell during virus replication

VSVDG-SARS-CoV-2 Process Development: Would the EREVEBO ® Process be Plug and Play?

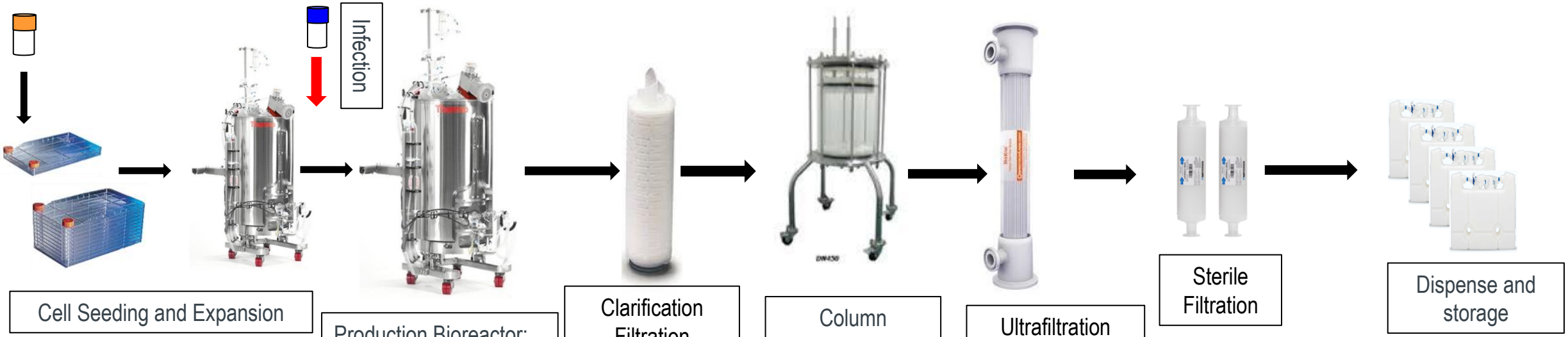
ERVEBO® Ph 3 Process



ERVEBO unit operations resulting in poor yields for SARS-CoV-2.

VSVDG-SARS-CoV-2 Phase 2/3 Process

Conversion to commercial-ready microcarrier process implemented in 3.5 months



Eliminates separate processing operation

Eliminates closed processing

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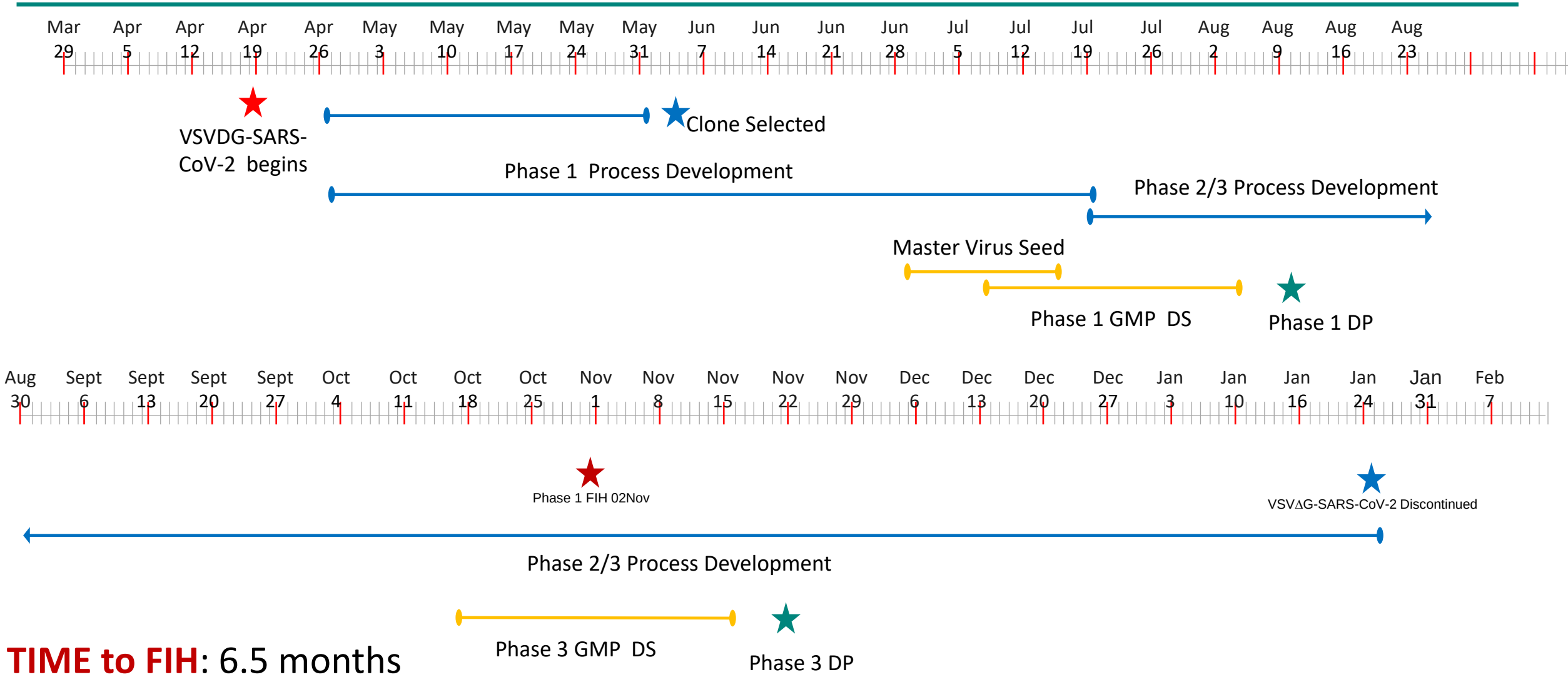
Moving with Speed: Development Timeline for VSVDG-SARS-CoV-2



TIME to FIH: 6.5 months

TIME to Ph3 READY: 6 months

Lessons Learned to be Applied to Future Vaccine Development Programs

Process Development

- Platform processes with standard unit operations can enable faster path to clinic and commercial manufacture
- Early Integration with Discovery to enable optimum clone selection considering both antigenicity and manufacturability
- Minimize repeat scientific work and take reasonable risk-based decisions in development
- Front-load analytical resources to enable rapid process understanding.

Manufacturing

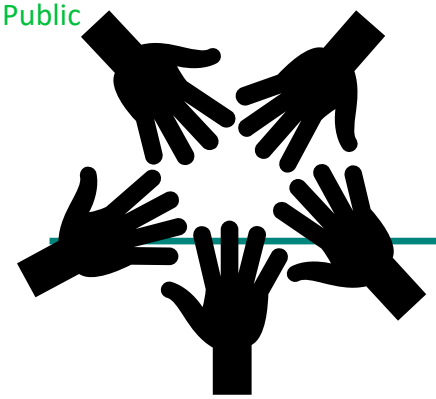
- Use existing facilities to support PPQ activities and address long term commercial capacity off critical path
- Design and implement multi-purpose flexible facilities

Clinical and Regulatory Interactions

- Up-front understanding of clinical dose impact on manufacturability and timelines
- Technical reports are source documents and “rolling” submissions can accelerate regulatory pathways
- Early engagement with the regulatory agencies for alignment on strategies for product development and licensure
- Recognize each country has unique regulatory requirements

Emergency Use Authorization

- Requires advance planning to establish fastest path to clinical efficacy PoC
- Quality must not be compromised; EUA does not “shortcut” this!
- Manufacturers must comply with existing regulations



We’re all under the same pressure to get it right and to obtain the approvals to ensure availability of licensed doses to support ongoing outbreak efforts.

Acknowledgements

Merck Ebola Team

Merck COVID Team

VPR&D organization

Joe Joyce

Brendan Grau

Doug Richardson

Kim Hassis

Liman Wang

External partners – IAVI, GAVI, UNICEF, WHO to name a few

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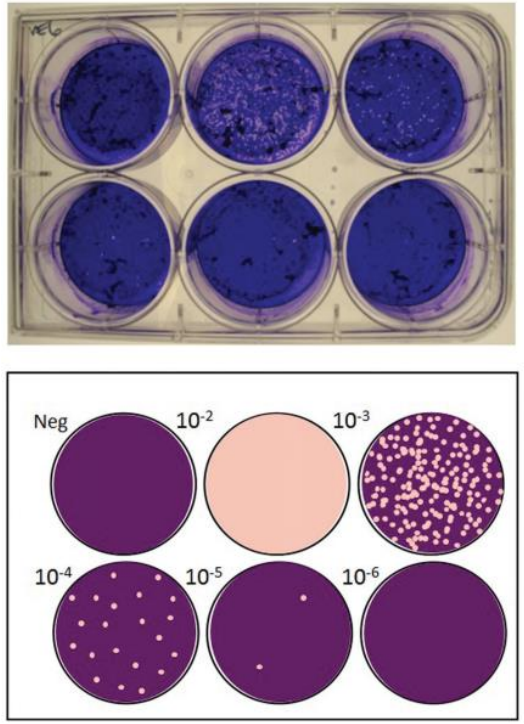
Back-Ups

Automation to Accelerate LVV Process Development

Standard Plaque assay

- 1 to 24-well format
- Manual assay and visualization
- Crystal Violet stain (clear spots = plaques)

Plaque Assay Layout Example

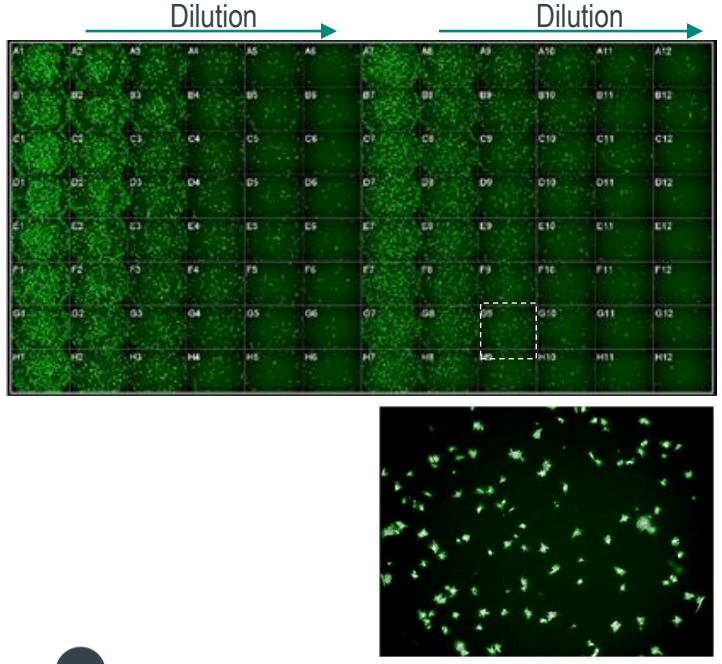


µPlaque Assay

- 96-well format
- Automated assay and imaging
- Immunofluorescence staining for viral proteins
  - Viral Nucleoprotein (NP)

HighRes Biosolutions System "Phoenix"

µPlaque Assay Layout Example



Mendoza, *et al. Curr. Prot. Microbiol.* 57, 2020.

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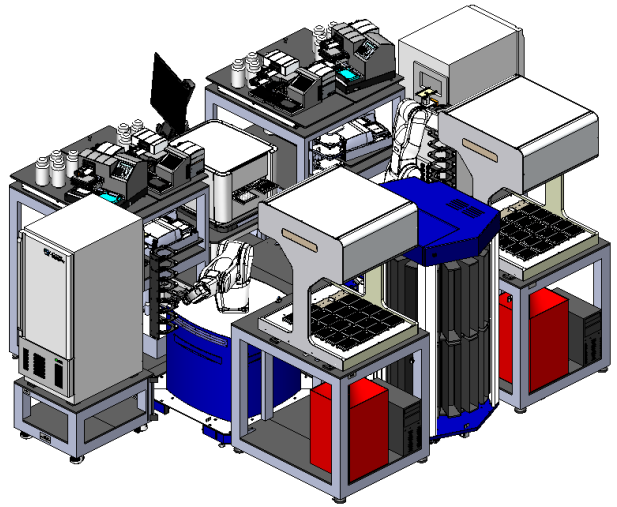
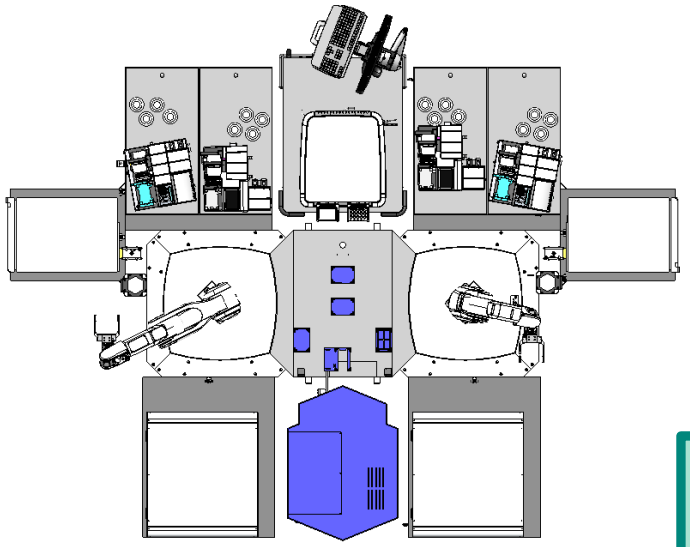
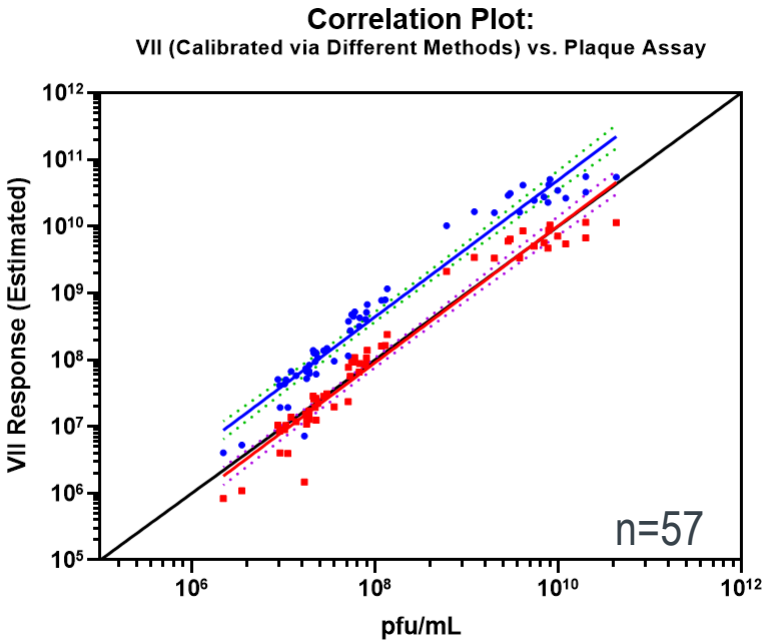
Automation to Accelerate LVV Process Development

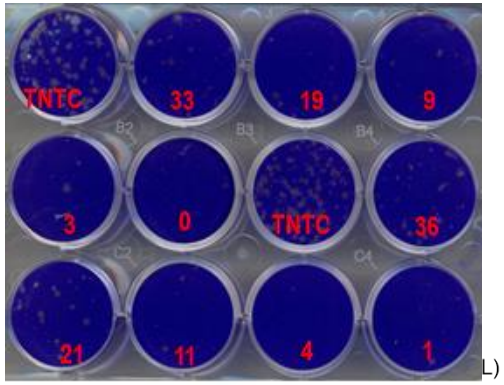




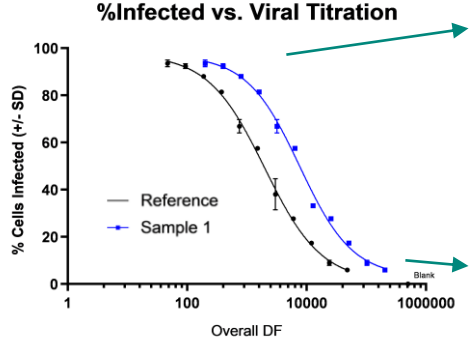


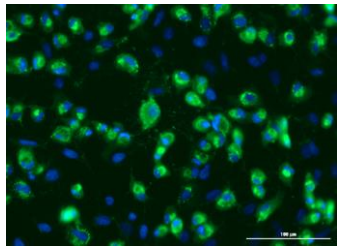
Assays are ***correlative***

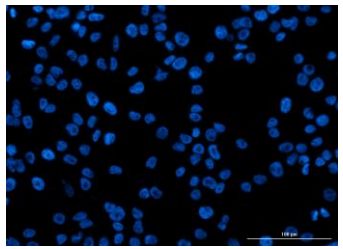
- R = **0.97** (strong positive correlation)



12w Plaque plate







HTA enables:

1. Directionally and speed
2. Consistency and predictive with release assays

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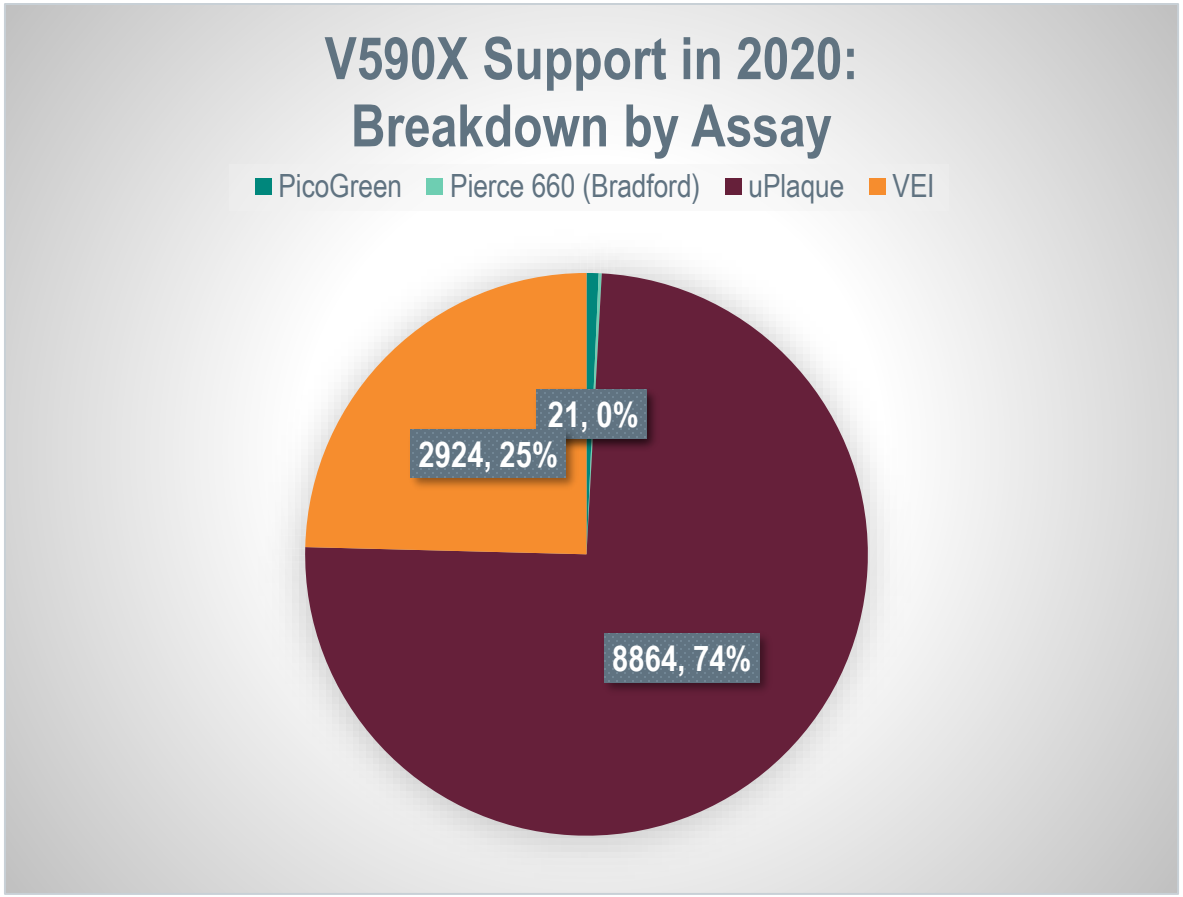
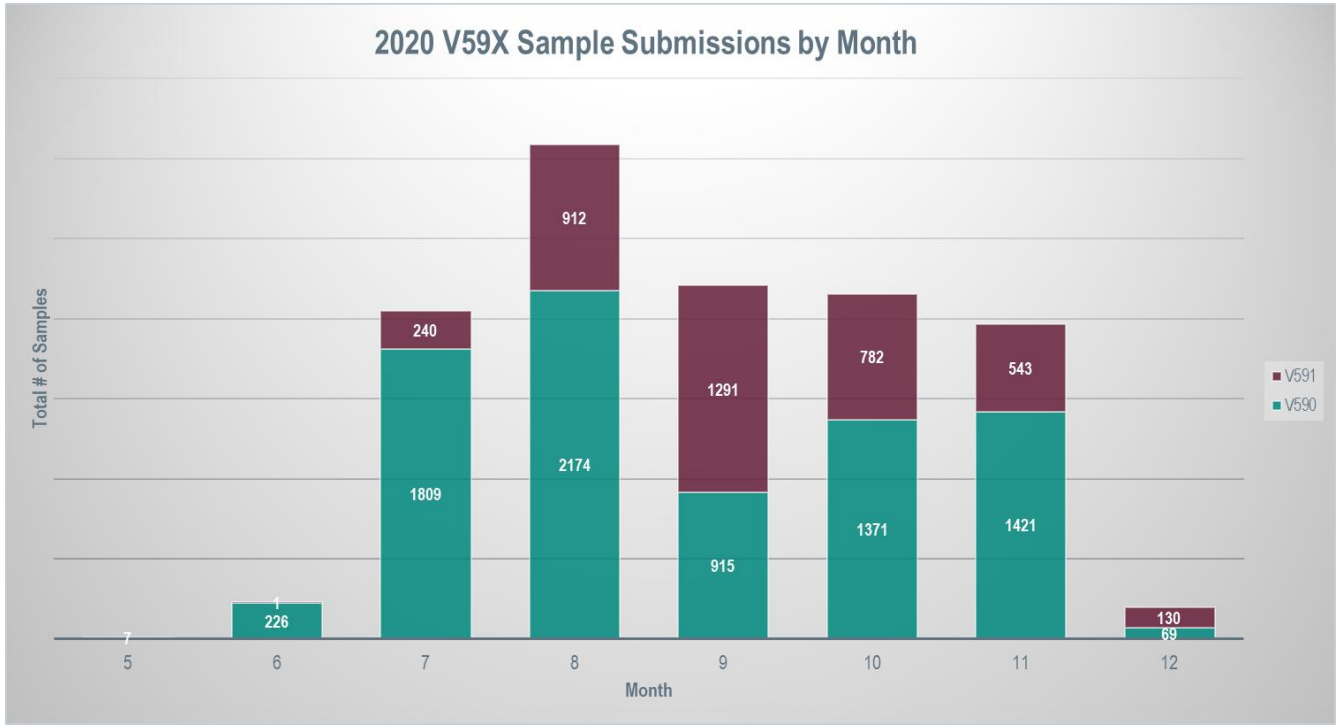
Automation to Accelerate LVV Process Development





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Next Gen Sequencing and Viral Metagenomics for LVV

- ➢ Master virus seed and Ph I bulk harvests tested in limited VMA to due to lack of adequate AVA neutralizing antibody
- ✓ Sequencing met or exceeded depth requirements from regulators.
- ✓ Spike virus recovery was consistent across samples and demonstrated reasonable sensitivity.
- – Virus Master seed study had a bioinformatically-confirmed contig sequence 'hit' to another virus in the infected harvest

Vaccine virus-infected		Control Cells		Reagent Controls	
Infected cell pellet	Infected harvest	Uninfected cell pellet	Uninfected fluids	Medium control	Cell wash (PBS) control
0	8,913 nucleotides	0	0	0	0

But the other virus *was not detected* in

1. Other samples in either MVS or bulk
2. Original cell substrate VMA or production samples
3. Harvest or fluids samples using RT-QPCR for that particular virus

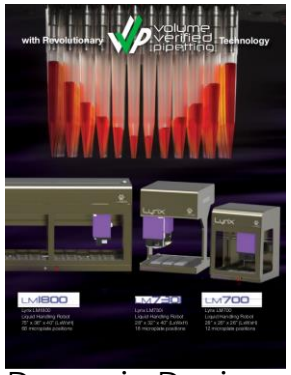
❖ **Assignable cause determined**:

- The dual index used for infected harvest was the same as the index two runs prior on same NextSeq instrument!
- The project was to conduct complete genome sequencing on that particular virus, **so carryover was the source.**

➢ **Lesson: Implementation of dedicated indices for our samples at the sequencing lab.**

➢ **Conclusion**: VMA supported a low viral risk of the cell substrate, seed, and bulk, thus complementing a partial gap in the risk profile based on conventional testing.

Vaccine HTA Instrumentation



Dynamic Devices
Lynx VVP
Preanalytical sample prep

Tecan Freedom EVO 2M (96/384)
Biochem and ELISA – 9 plates

Hamilton Vantage (384)
ELISA – 24 plates

Sartorius CompacT Cell Culture System
Flask handling, cell passaging

HRB "Phoenix"
CBA – 36 plates

PAA "Helios"
CBA – 60 plates

HRB "Selene"
CBA – 60 plates
Multi-assay

Instrument Complexity & Capacity

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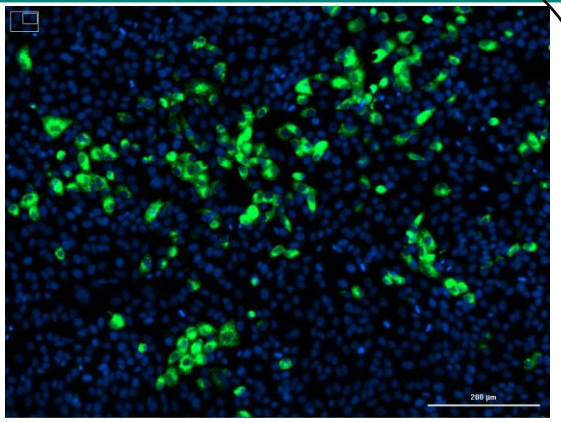
HTA Cell Based Platforms

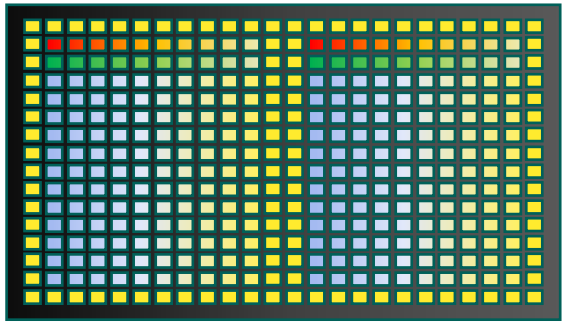
HighRes Biosolutions System "Selene"



V590 Infectivity using BioTek Cytation5

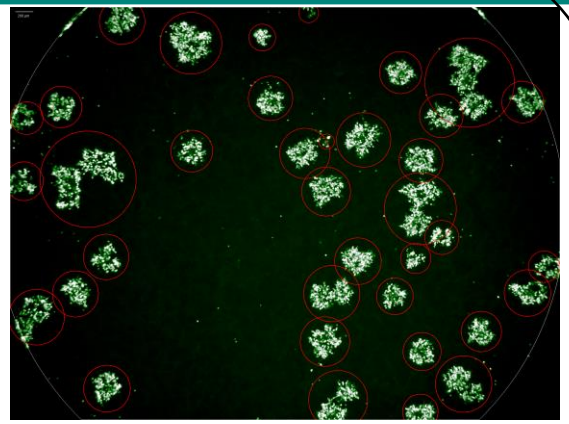
HT Infectivity Assay Platform

- Fully automated (48-60) 384 well plate run capacity – 12 samples/plate (in duplicate)
- 576 - 720 samples per run
- 2-3 runs/week
- 96-capacity built-in
- BioTek Cytation5



Our first HighRes Biosolutions System "Phoenix" →
Set up for both Assay Platforms in lower capacity and throughput

PAA System "Helios"



V590 Immuno-plaque
Image captured using PE EnSight (Algorithm Counted: 44)

HT uPlaque Assay Platform

- Fully automated (44-48) 96 well plate run capacity – 14 samples/plate (in singleton)
- ~600-700 samples per run
- 1-2 runs/week
- 384 well capability built-in
- PE EnSight & BioTek Cytation3