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

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Vaccine Process Development & Commercialization

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Outline

Background

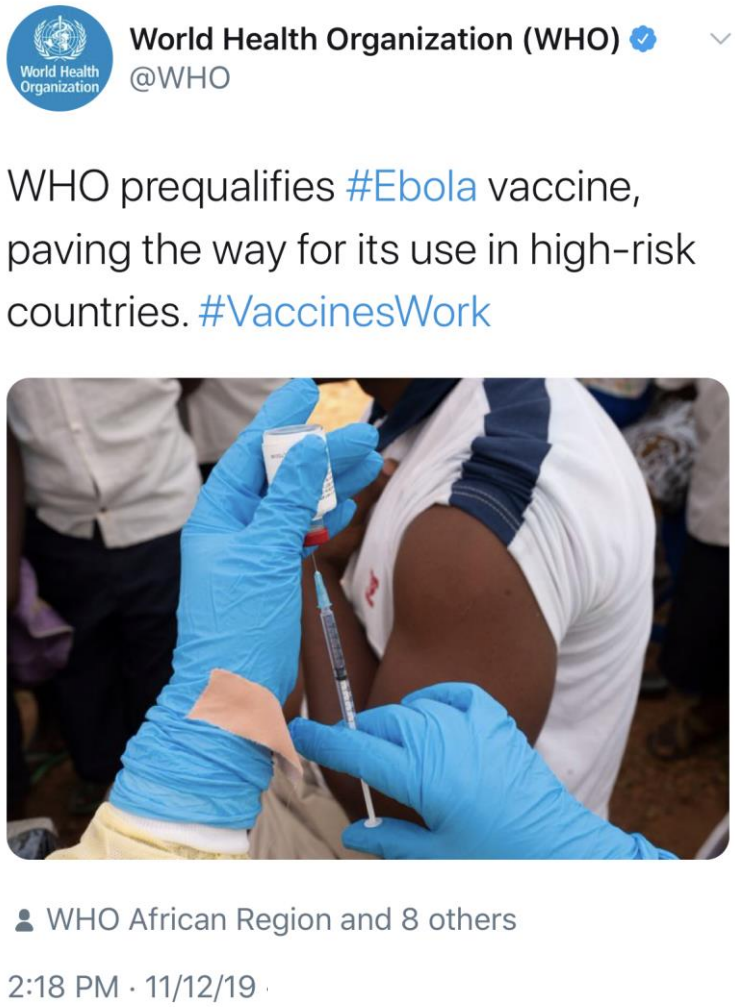
- Ebola virus outbreak 2014-2016
- Ervebo® brief timeline

Development and Tech Transfer

-Analytical comparability

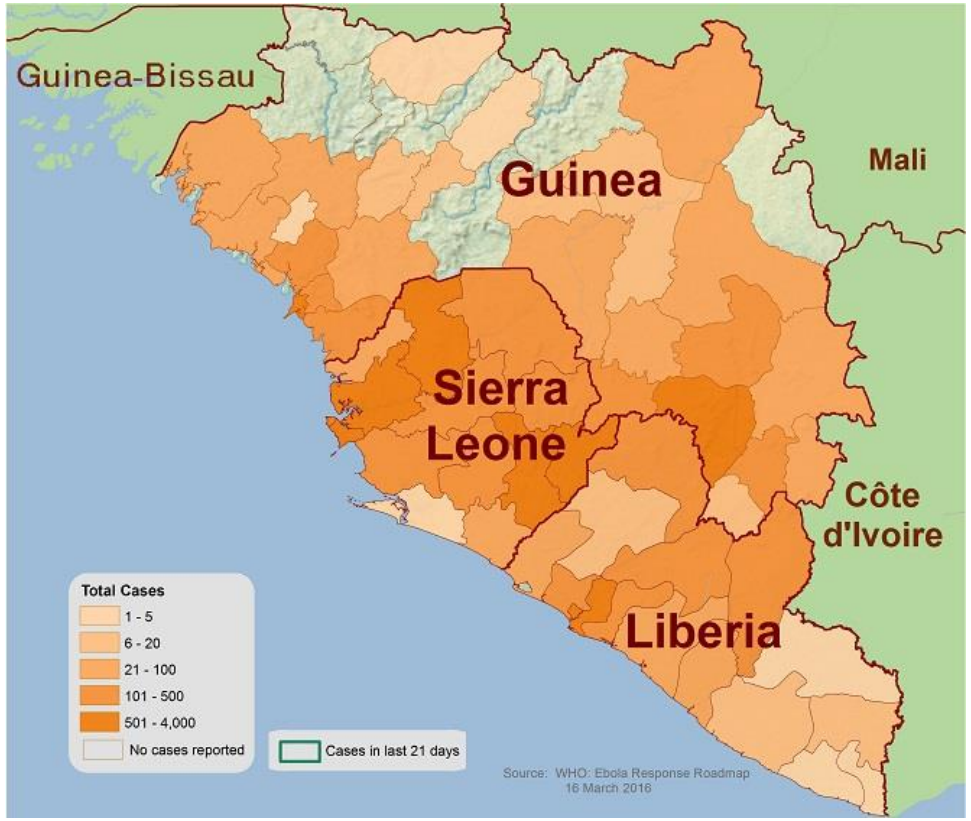
-Approaches to accelerate

Key Takeaways



2014-2016 Outbreak

Total Cases as of 16Mar2016 (latest update)



<u>World Health Organization</u>:
"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

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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

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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

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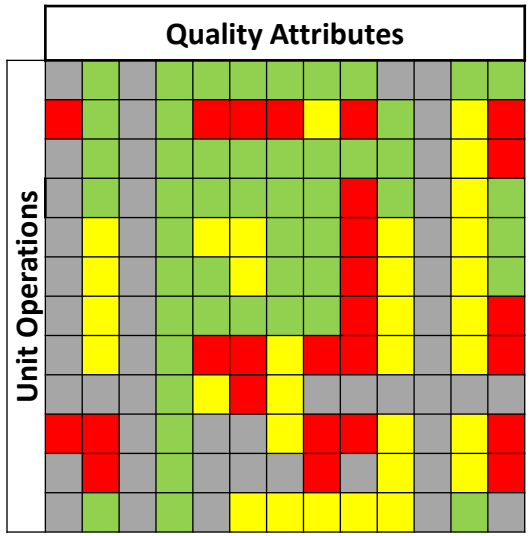
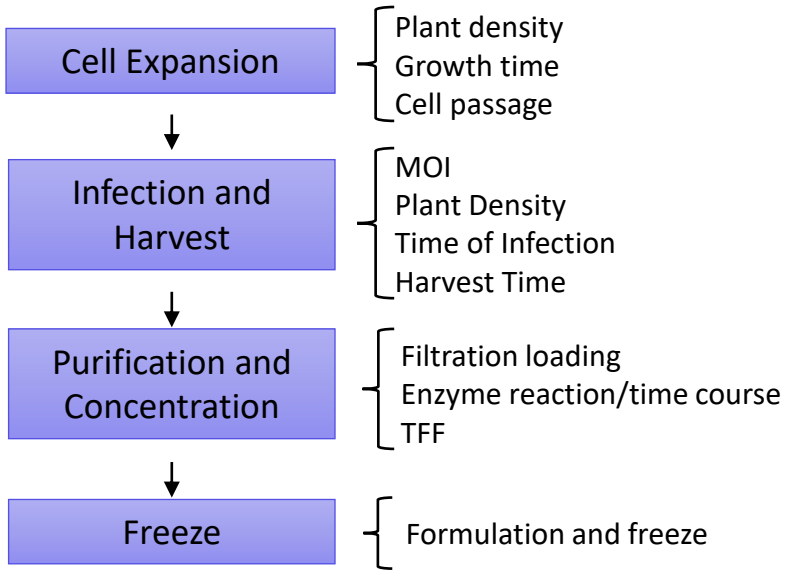
Approaches to Accelerate

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

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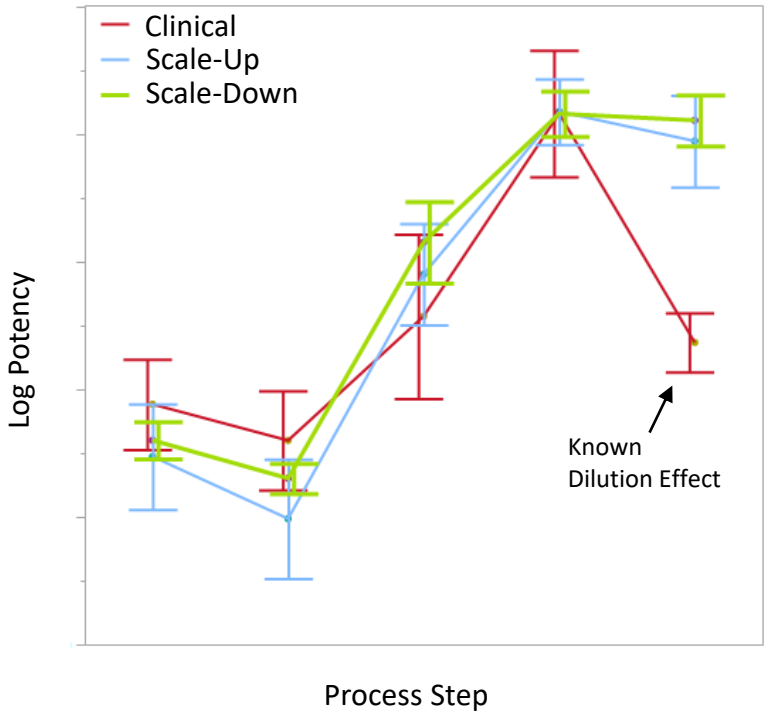
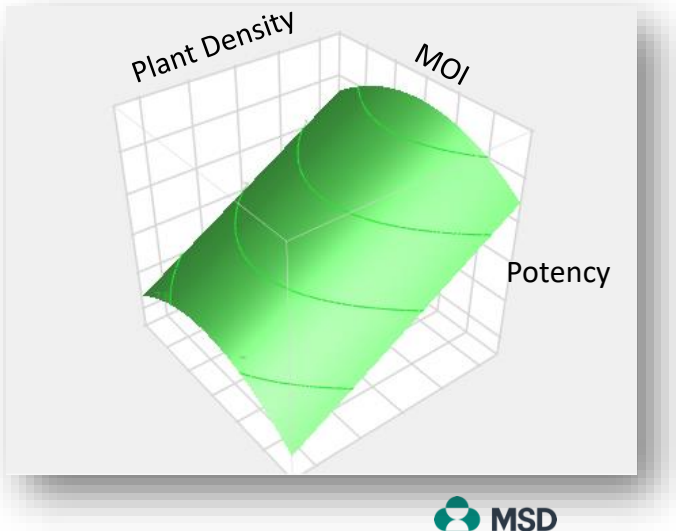
Approaches to Accelerate

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

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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

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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)

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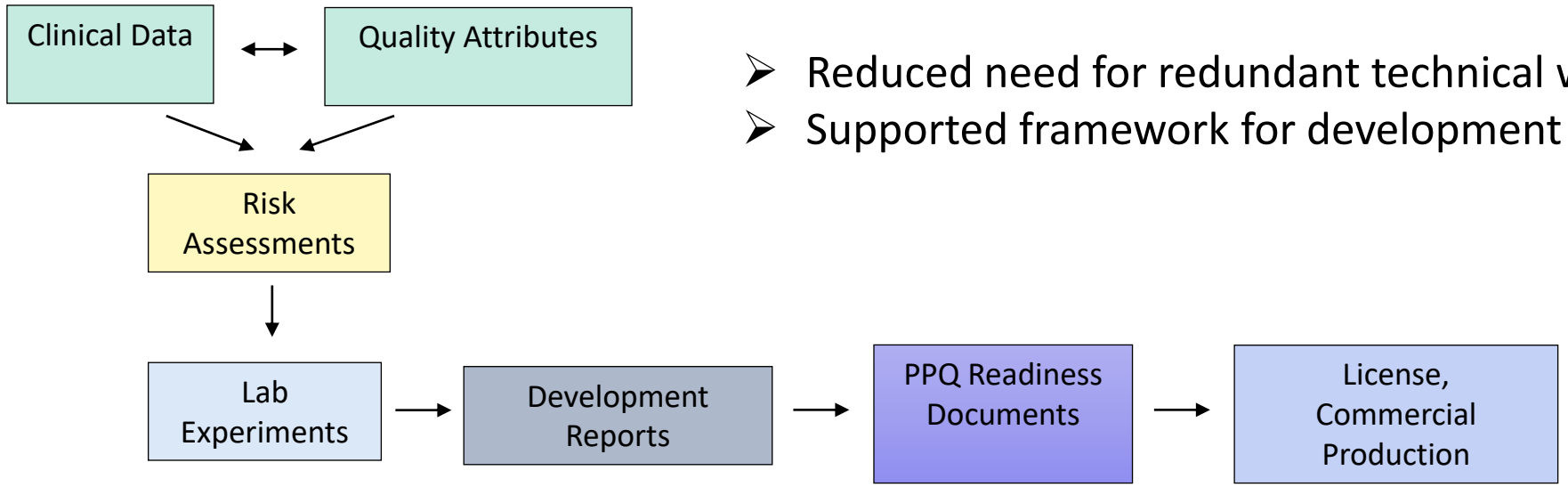
Approaches to Accelerate

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

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Approaches to Accelerate

Regulatory Designations Enabled Enhanced Interactions

- Food and Drug Administration (FDA) **Breakthrough Therapy Designation**
- European Medicines Agency (EMA) Priority Medicines (**PRIME**) status
- WHO Prequalification Roadmap[1]

Food and Drug Administration (FDA)
Fast Track or Breakthrough Therapy designations

European Medicines Agency (EMA)
Priority Medicines (PRIME) status

- Multiple meetings to review CMC plans (23 meetings from 2015-2019
- Rolling submission of CMC dossier sections
- Submit to EMA + WHO + African Health Authorities simultaneously
- Pre-Licensure inspections prior to completion of all PPQ batches

[1]https://www.who.int/medicines/news/2019/roadmap_for_intro_roll_out_licensed_ebola_vaccine/en/

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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
- Enhanced interactions with health authorities

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Thank you!