

# Ervebo<sup>®</sup> vaccine for Ebola virus – a case study on approaches to accelerate process development and tech transfer

Joseph P. Califano, PhD

Vaccine Process Development & Commercialization

# Outline

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## Background

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

## Development and Tech Transfer

- Analytical comparability
- Approaches to accelerate

## Key Takeaways



World Health Organization (WHO) ✓

@WHO

WHO prequalifies [#Ebola](#) vaccine, paving the way for its use in high-risk countries. [#VaccinesWork](#)

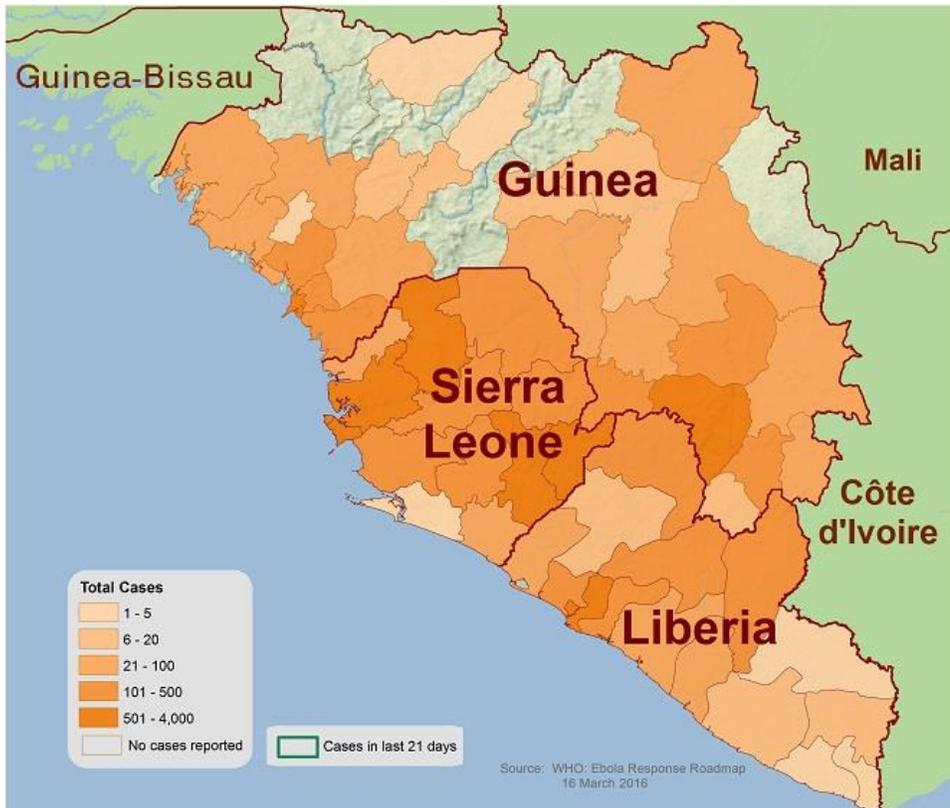


WHO African Region and 8 others

2:18 PM · 11/12/19 ·

# 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

## Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

Ana Maria Henao-Restrepo, Anton Camacho, Ira M Longini, Conall H Watson, W John Edmunds, Matthias Egger, Miles W Carroll, Natalie E Dean, Ibrahim Diatta, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Erwere, Rebecca Grais, Stephan Gunther, Pierre-Stéphane Gsell, Stefanie Hossmann, Sara Vilsboen Wastle, Mandy Kader Kondé, Sakoba Kéita, Souleymane Kone, Ewa Kuisma, Myron M Levine, Sema Mandal, Thomas Mautz, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, John-Arne Rattingen, Marie-Paule Kieryn\*

### Summary

Background: rVSV-ZEBOV is a vaccine against Ebola virus disease (EVD) that has been shown to be safe and effective in a phase 1/2 trial in Guinea.

Methods: We conducted a cluster-randomised, open-label, ring vaccination trial in Guinea. The trial was designed to evaluate the efficacy and effectiveness of rVSV-ZEBOV in preventing EVD in a high-risk population.

Results: The trial included 10,000 participants in 10 clusters. The vaccine was highly effective in preventing EVD in the trial population.

Conclusions: The rVSV-ZEBOV vaccine is highly effective in preventing EVD in a high-risk population. This vaccine has the potential to significantly reduce the burden of EVD in high-risk areas.

Keywords: Ebola virus disease, vaccine, efficacy, effectiveness, Guinea, ring vaccination, open-label, cluster-randomised trial.

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WHO/15/MSD.1. For more information on this trial, please visit <http://www.who.int/news-room/detail/12-11-2015-who-prequalifies-ebola-vaccine-paving-the-way-for-its-use-in-high-risk-countries>.

WHO/15/MSD.1. For more information on this trial, please visit <http://www.popsoci.com/best-of-whats-new-2015/healthcare>.

WHO/15/MSD.1. For more information on this trial, please visit <http://www.who.int/news-room/detail/12-11-2019-who-prequalifies-ebola-vaccine-paving-the-way-for-its-use-in-high-risk-countries>.

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## 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

**World Health Organization**  
20, AVENUE APPIA - CH-1211 GENEVA 27 - SWITZERLAND - TEL CENTRAL +41 22 791 2111 - FAX CENTRAL +41 22 791 3111 - WWW.WHO.INT

Tel direct: +41 22 791 5531  
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In reply please (8-370-43 AMRO refer to: PQT-GE/rs (2019-281)

Your reference:

Dr Jules Milligo  
Director, Public Health Partnerships  
Global Vaccines  
Merck & Co., Inc.  
351 North Sumneytown Pike  
North Wales, PA 19454  
Etats-Unis d'Amérique

12 NOV 2019

Dear Dr Milligo,

Acceptability, in part attenuated, Recombinant for V

We are pleased to announce that the ERVEBO (Ebola Zaire Virus (rVSV) based vaccine, Kikwit 1995 strain surface

**EUROPEAN COMMISSION**  
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY  
Directorate B - Health systems, medical products and innovation  
B5 - Medicines - policy, authorisation and monitoring  
Head of unit

Brussels, 11 November 2019

NOTE TO THE MEMBERS OF THE STANDING COMMITTEE ON MEDICINAL PRODUCTS FOR HUMAN USE/STANDING COMMITTEE ON VETERINARY MEDICINAL PRODUCTS

Subject: Adoption of COMMISSION IMPLEMENTING DECISION granting a conditional marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council "Ervebo - Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live)", a medicinal product for human use

**FDA U.S. FOOD & DRUG ADMINISTRATION**

Our STN: BL 125690/0

**BLA APPROVAL**  
December 19, 2019

Merck Sharp & Dohme Corp.  
Attention: Jayanthi Wolf, PhD  
351 N. Sumneytown Pike  
P.O. Box 1000  
UG2D-068  
North Wales, PA 19454

Dear Dr. Wolf:

Please refer to your Biologics License Application (BLA) submitted on July 12, 2019, and received on July 15, 2019, under section 351(a) of the Public Health Service Act (PHS Act) for Ebola Zaire Vaccine, Live.

**LICENSING**

We have approved your BLA for Ebola Zaire Vaccine, Live effective this date. You are

# Development and Tech Transfer Challenges and Goals

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**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

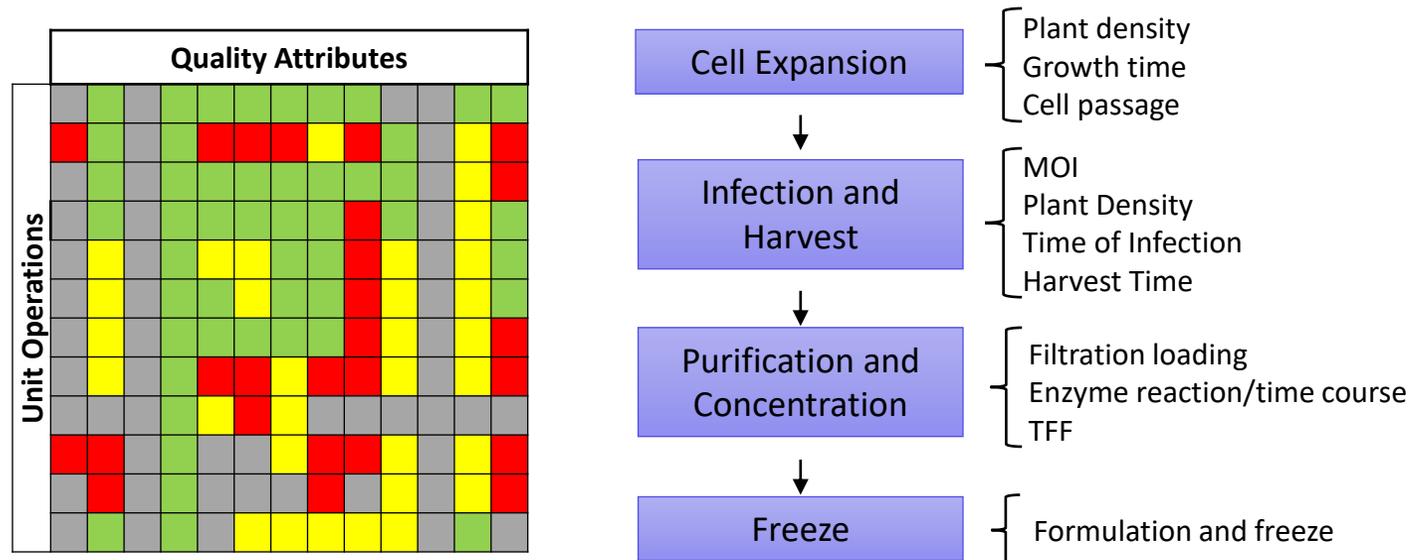
## 3. Commercial

-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

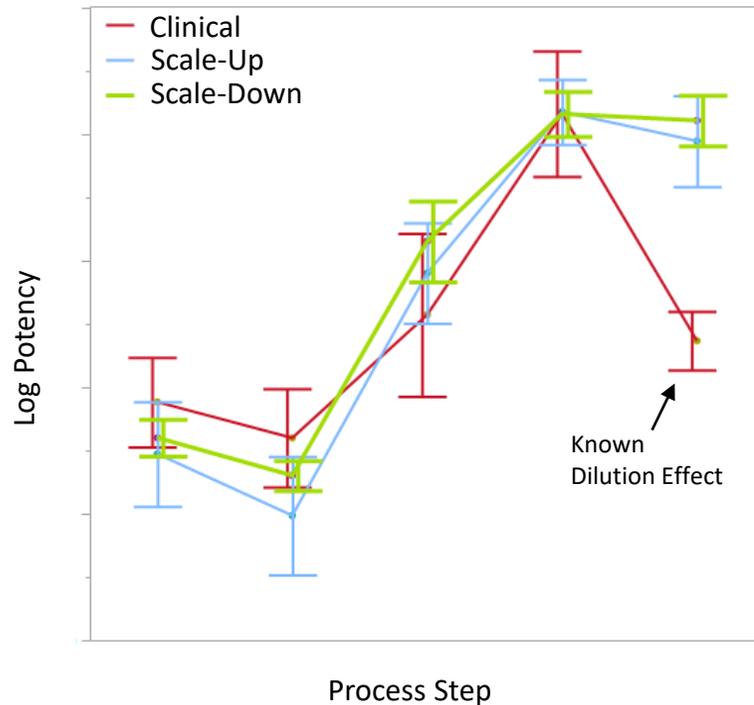
## Use a Risk-Based Approach to Prioritize Experiments; Leverage Prior Knowledge



- 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

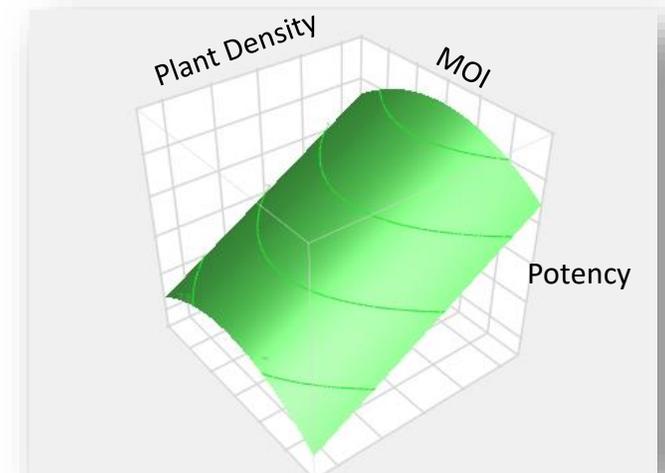
# Approaches to Accelerate

## Develop a Scale-Down Model for Experimental Work



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

- 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



# 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

# Approaches to Accelerate

## Develop a Single-Use Drug Substance Process



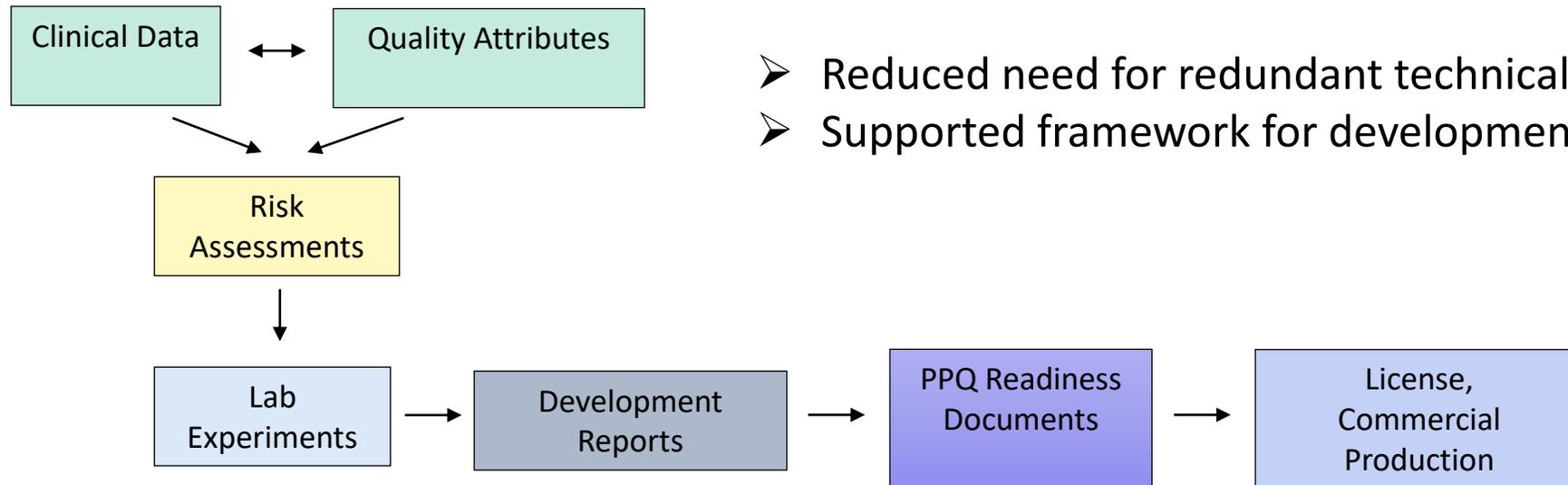
PFD, process flow diagram  
URS, user requirement specification  
RFP, request for proposal  
VOC, voice of customer



- 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

# 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<sup>1</sup>
- 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



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



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



World Health  
Organization

# Key Takeaways

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Several approaches were used to accelerate process development and tech transfer of Ervebo<sup>®</sup>:

- 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 “hypercure” support of PPQ and commercial manufacturing
- Enhanced interactions with health authorities

# Acknowledgements and Thanks

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- 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.





Thank you!