

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

Outline

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](#)

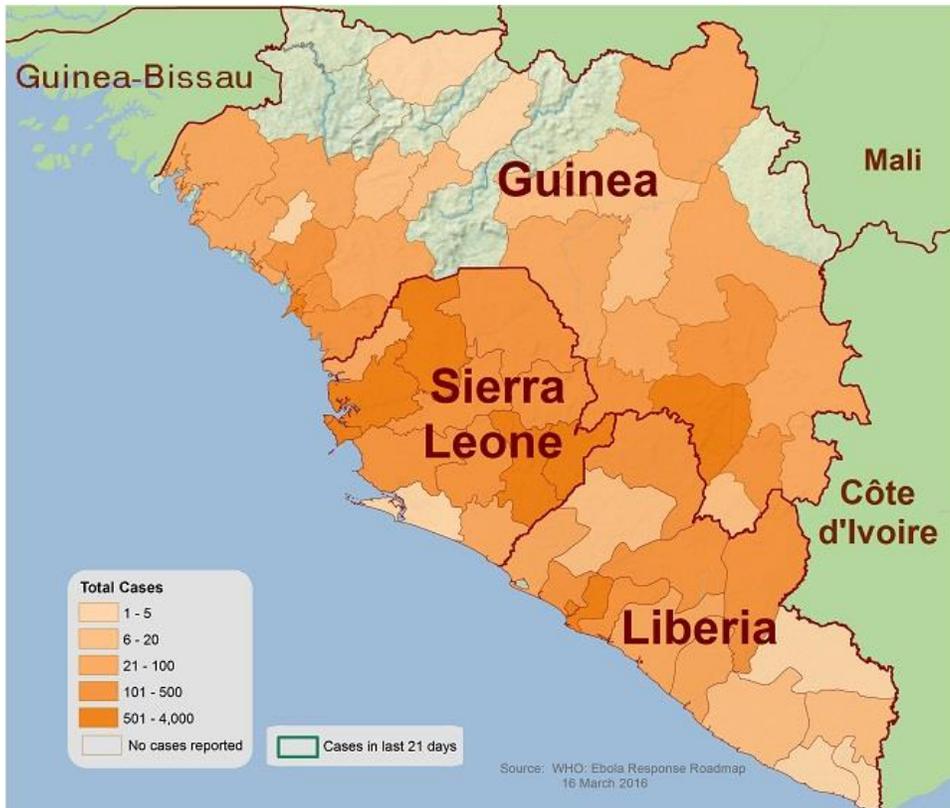


WHO African Region and 8 others

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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 Gosselin, Stefanie Hossmann, Sara Vilsboeren Wastle, Mandy Kader Kondé, Sakoba Kéita, Souleymane Koné, 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 trial. It is now being evaluated in a large-scale, open-label, cluster-randomised trial in Guinea.



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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 particular, of attenuated, Recombinant for V

We are pleased to announce that 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



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

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.popsi.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

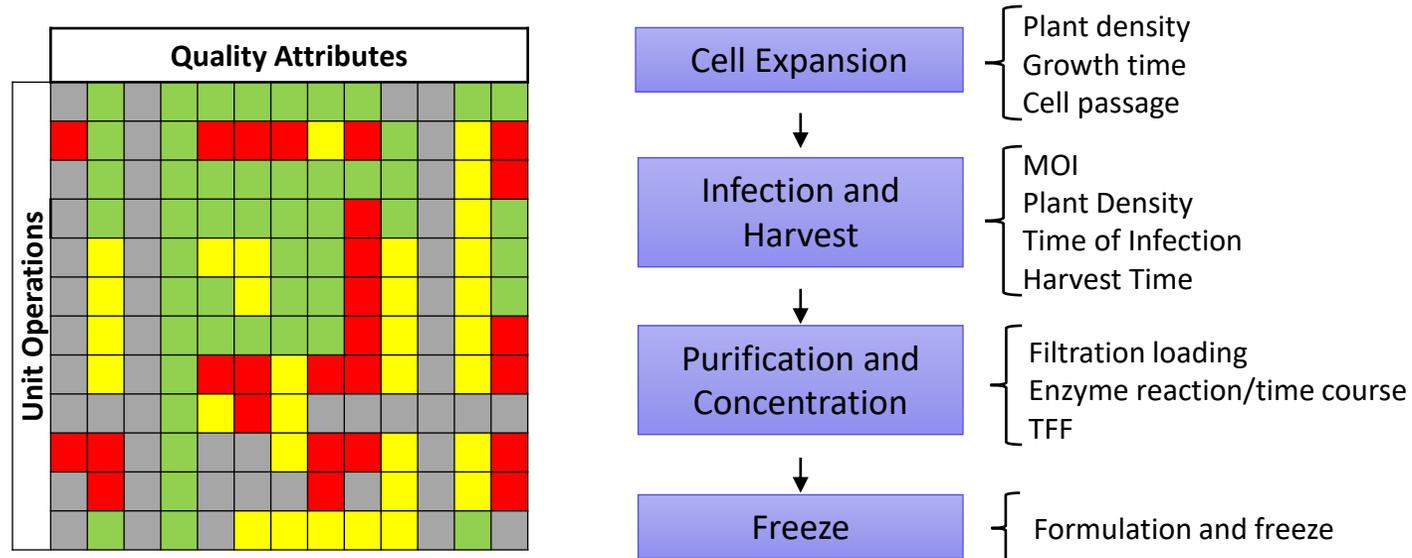
3. Commercial

-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

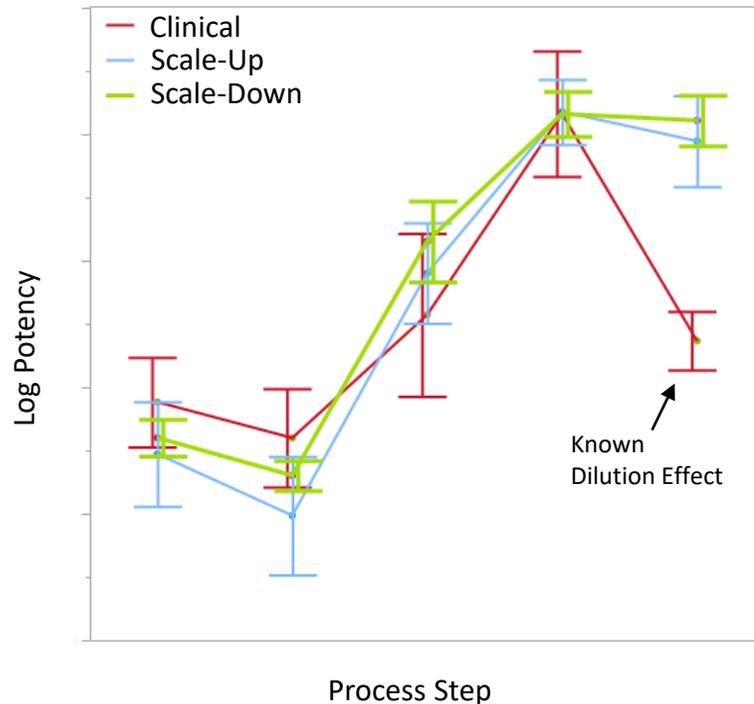
Use a Risk-Based Approach to Prioritize Experiments; Leverage Prior Knowledge



- 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

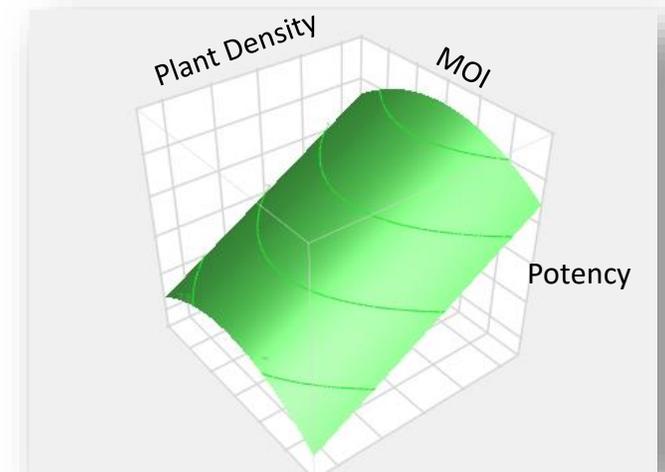
Approaches to Accelerate

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



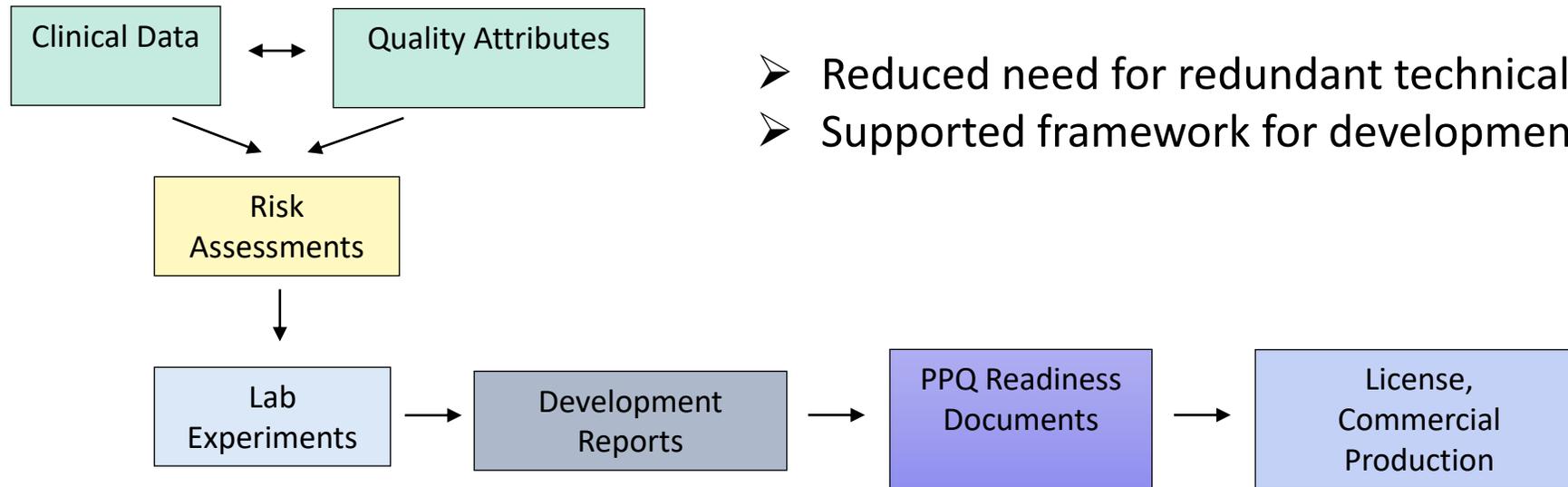
PFD, process flow diagram
URS, user requirement specification
RFP, request for proposal
VOC, voice of customer



- 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 Roadmap¹
- 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

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

Acknowledgements and Thanks

- Study volunteers and study investigators
- Our many external partners, collaborators, and funding organizations
- Ervebo® product development team, sub-teams, leadership
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Thank you!