Objectives – CMC Perspective

ERVBO® Ebola Zaire Vaccine, Live
Overview of accelerated review and approval

Case Study
• The plan
• What happened

Lessons
What Went Well and Opportunities for Improvement
Product information: ERVEBO® is a recombinant, replication-competent, vesicular stomatitis virus (VSV)-vectored-vaccine containing the glycoprotein of Zaire ebolavirus (ZEBOV)

The Vaccine: rVSVΔG-ZEBOV-GP rVSV expressing envelope GP of the Zaire Ebola virus species (Kikwit variant)

Product class: Vaccine for active immunization of individuals 18 years of age or older to protect against Ebola virus disease (EVD) caused by Zaire Ebola virus

Geographical region: Clinical trials were conducted in Africa, North America and Europe
Product Development Overview

• In November 2014, Merck and NewLink Genetics Corp. entered into an exclusive worldwide license agreement wherein Merck assumed responsibility to research, develop, manufacture, and distribute the investigational Ebola vaccine candidate (rVSVΔG-ZEBOV-GP, referred to as V920)

• Merck, NewLink Genetics, and a global network of partners are collaborating in unprecedented ways with the singular focus of speeding the research, development, and deployment of a well tolerated and effective Ebola vaccine

• The efforts of all of our partners in the midst of the largest Ebola epidemic in history highlight what we, as a public health community, can accomplish when we work together
Extensive Partnerships and Alliances

**Phase I Studies**

- **N=8**
  - WHO Clinical Consortium/Wellcome Trust
  - **Switzerland:** University Hospitals of Geneva
  - **Germany:** University Medical Center Hamburg/Clinical Trial Center North
  - **Gabon:** Centre de Recherches Medicales de Lambarene/University of Tuebingen
  - **Kenya:** Kenya Medical Research Institute Marburg Laboratory
  - **CCV** – Halifax, Canada
  - US Department of Defense (WRAIR, JVAP, USAMRIID, DTRA)
  - **NIAID/NIH**
  - **NewLink Genetics**

*Funding & support from BARDA*

**Phase II/III Studies**

- **N=5**
  - Liberia (PREVAIL): Liberia – NIH Partnership (NIAID)
  - Sierra Leone (STRIVE): CDC/Sierra Leone Medical School/BARDA
  - Guinea (Ebola ça suffit and Front-Line Workers): WHO/Norwegian Institute of Public Health/MSF/HealthCanada
  - US/Canada/Spain (V920-012): Merck/BARDA

*Additional Funding & Support:*

- US Department of Health and Human Services (BARDA)
- US Department of Defense (DTRA, JVAP)

Confidential
Manufacturing sites

Clinical trial supplies were made at a Contract Manufacturing Organization.

Additional clinical supplies and recent outbreak doses were made in a Merck Biological Pilot Plant (BPP).
Accelerated Reviews and Approvals – the Regs
Regulatory Designations to Expedite Development

Enhanced support for the development of medicines that **target an unmet medical need for life-threatening diseases with major public health interest**

- **Breakthrough Therapy Designation** and **PRIME**

Enable **formal and consistent dialog/interactions with regulators** on product development and aligning on processes/timelines **prior to filing**

Granted based on **evidence that the candidate demonstrates potential to address unmet medical need**

- Breakthrough Therapy designation requires preliminary clinical evidence
WHO Prequalification Collaborative Review

Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines

- Designed to use available scientific expertise and human and financial resources to decide, with reasonable certainty, on the benefit–risk profile of an evaluated product when used in a given country

- **Roadmap** established for the Merck Ebola Vaccine
  - Each NRA selects the approach that will make best use of the resources, workload and competence of individual NRAs (**no sequential steps** following NRA approval or **sequential steps** following NRA approval)
  - NRA approval timing can range from completely independent data reviews and inspections to adoption of regulatory decisions of reference authorities without any further scientific review
# Review Comparisons

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<thead>
<tr>
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<th>Standard Review Period</th>
<th>Accelerated Review Period</th>
<th>ERVEBO® Experience</th>
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<tbody>
<tr>
<td><strong>FDA</strong></td>
<td>6 to 10 months</td>
<td>6 months (Priority Designation)</td>
<td>~3 months</td>
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<td><strong>EMA</strong></td>
<td>210 days (12 to 14 months to obtain MA)</td>
<td>150 days (8 months to obtain MA)</td>
<td>~8 months to obtain Conditional MA</td>
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<td><strong>WHO Prequalification</strong></td>
<td>Median consistently 200 days following NRA approval</td>
<td>Shortly following NRA approval</td>
<td>1 day following NRA approval</td>
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<td><strong>Participating NRAs (individual countries participating)</strong></td>
<td>Varies – typically 2-4 years following NRA approval</td>
<td>Maximum 90 days following NRA approval (per roadmap)</td>
<td>Ongoing – earliest obtained 39 days following NRA approval</td>
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CASE STUDY
THE CMC STORY
The Plan

Multiple meetings to review CMC plans
- Facility design and qualification
- Process qualification
- Analytical characterization and release testing strategy and locations

Rolling submission of CMC dossier sections
- Complete PPQ at the commercial facility during review
- Review draft M3 sections prior to submission

Submit to EMA + WHO + African Health Authorities simultaneously
- Same level of CMC detail to WHO and African Health Authorities

Pre-Licensure inspections prior to completion of all PPQ batches
- FDA
- EMA / WHO / AVAREF / GAA
What Happened – Agency Interactions

Enhanced interaction and early dialogue to optimize development plans and speed up evaluation so these medicines can reach patients earlier.

Between 2015-2019 there were 23 meetings (formal and informal) where CMC topics were discussed

<table>
<thead>
<tr>
<th>Year</th>
<th>FDA</th>
<th>EMA/WHO</th>
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<tbody>
<tr>
<td>2015</td>
<td>3</td>
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<tr>
<td>2016</td>
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<td>2018</td>
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<tr>
<td>2019</td>
<td>4</td>
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What Happened – FDA Submission Timetable

**Pre-BLA Meeting**
- **11-Oct-2018**

**CMC-1**
- **12-Dec-2018**
- **Pre-License Inspection**
  - **18 to 26-Feb-2019**

**CMC-2**
- **12-15-Jul-2019**
- **Priority Review Granted**
  - **12-Sep-2019**
- **BLA Approval Granted**
  - **19-Dec-2019**

**Filing Review Period**
**PDUFA Priority Review Period**
**PDUFA Approval Date:**
- **Mar-2020**

**Rolling BLA Submission**

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19 - CMC Requests for Information and CMC Amendments
- ~40 questions requiring written responses
What Happened – EMA (and WHO) Submission Timetable

MAA Submission 08-Mar-2019

- Start Procedure 28-Mar-2019
- Assessment Report 28-May-2019
- List of Questions 25-Jun-2019
- EU GMP Inspection Jul-2019
- Assessment Report 12-Sep-2019
- List of Outstanding Issues 17-Sep-2019

Company Responses 13-Aug-2019

- Company Responses 24-Sep-2019

Company Responses 28-May-2019

- List of Questions 25-Jun-2019
- EU GMP Inspection Jul-2019
- Assessment Report 12-Sep-2019
- List of Outstanding Issues 17-Sep-2019

CHMP Opinion 17-Oct-2019

- Assessment Report 10-Oct-2019
- European Commission Decision 11-Nov-2019
- List of Outstanding Issues 17-Sep-2019

WHO PQ 12-Nov-2019

- Assessment Report 10-Oct-2019
- European Commission Decision 11-Nov-2019
- List of Outstanding Issues 17-Sep-2019

Company Responses 12-Sep-2019

- Assessment Report 10-Oct-2019
- European Commission Decision 11-Nov-2019
- List of Outstanding Issues 17-Sep-2019

DRC Approval 23-Dec-2019

- Burundi Approval 20-Dec-2019
- Additional African Country Approvals (TBD 2020)

>100 CMC questions requiring written responses between LOQ and LoOI
Lessons

- **Feedback during meetings is not binding**
  CMC not as developed as in “normal” programs. Things will change:
  - Additional release tests and specifications required
  - Need to relocate release testing locations
  - Acceptance criteria (existing) revisited post PPQ execution

- **HA Inquiries coming at you from all sides**
  FDA – don’t know when questions are coming, 😞 but can negotiate timing to respond 😊
  EMA – know when questions are coming, 🙂 strict timing to respond 😞

- **Site operations stretched** to execute PPQ, support site inspections, and assist in HA responses simultaneously
Lessons

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.
**WHAT WENT WELL**

- Joint meetings, early reads on strategy
- Same dossier submitted to FDA, EMA, WHO, and African National Regulatory Authorities
- One set of inquiries from EMA/WHO and some participating NRAs
- FDA – able to send proposals via the IND, including draft M3 documents
- EMA – able to send proposals via EudraLink, including draft M3 documents
- Obtain informal feedback from the BWP
- Ability to Negotiate CMC-Related PMCs
- WHO PreQualification obtained shortly after EMA Conditional Approval

**OPPORTUNITIES**

- PRIME Kick-off meeting: Include the Co-rapporteur and the quality reviewers
- Joint meetings including both FDA and EMA
- One set of inquiries from both FDA and EMA
- Mutual Recognition of Inspections
Acknowledgements

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