EBOLA VACCINE CASE STUDY

ACCELERATED DEVELOPMENT AND REGISTRATION OF A VACCINE – A CMC PERSPECTIVE

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CASSS WCBP

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Objectives – CMC Perspective

ERVEBO® *Ebola Zaire Vaccine, Live*

Overview of accelerated review and approval

Case Study

- The plan
- What happened

Lessons

What Went Well and Opportunities for Improvement

ERVEBO®

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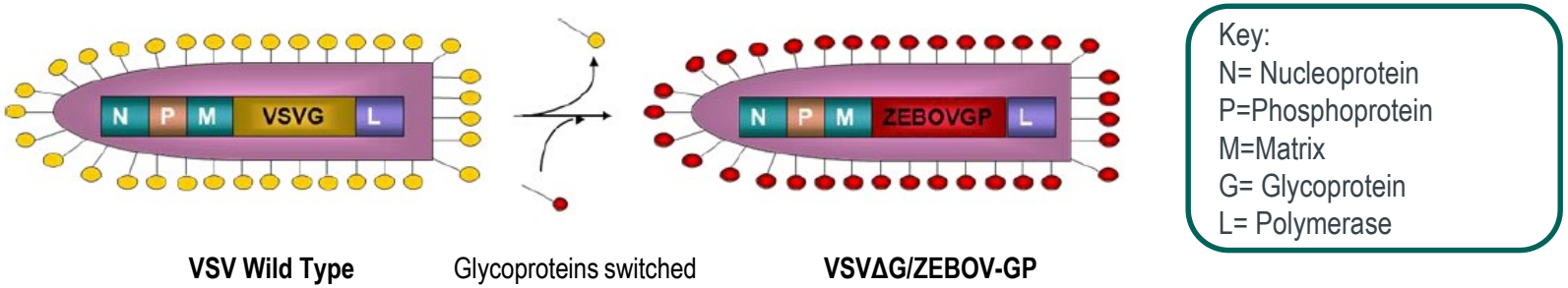
ERVEBO® (Ebola Zaire Vaccine, Live)

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

Public Health Agency of Canada

NewLink GENETICS

Phase I Studies
N=8

I

WHO Clinical Consortium/ Wellcome Trust

World Health Organization

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

II/III

- **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)

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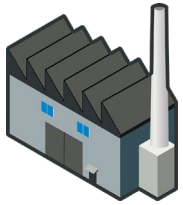
Manufacturing sites



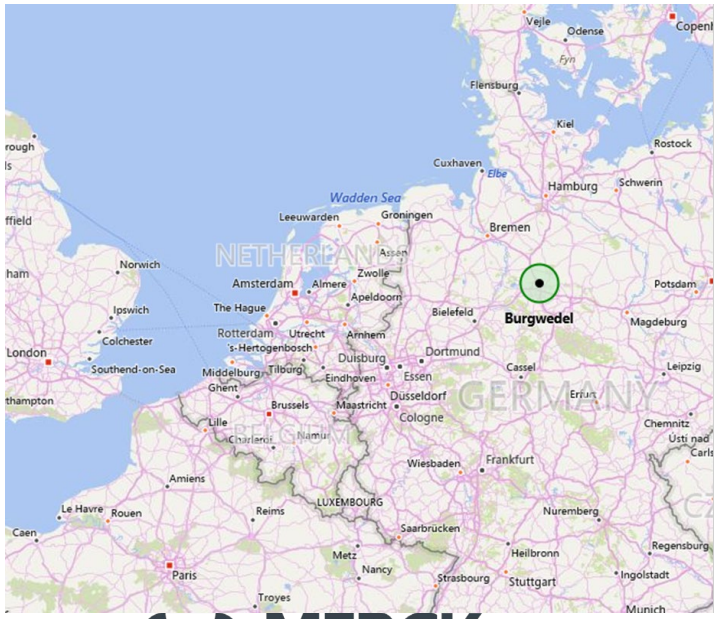
Clinical trial supplies were made at a Contract Manufacturing Organization

Process transfer & Scale Up

Additional clinical supplies and recent outbreak doses were made in a Merck Biological Pilot Plant (BPP)

Process transfer

Final Manufacturing Facility



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Accelerated Reviews and Approvals – the Regs

Regulatory Designations to Expedite Development

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

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

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

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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

	Standard Review Period	Accelerated Review Period	ERVEBO® Experience
FDA	6 to 10 months	6 months (Priority Designation)	~3 months
EMA	210 days (12 to 14 months to obtain MA)	150 days (8 months to obtain MA)	~8 months to obtain Conditional MA
WHO Prequalification	Median consistently 200 days following NRA approval	Shortly following NRA approval	1 day following NRA approval
Participating NRAs (individual countries participating)	Varies – typically 2-4 years following NRA approval	Maximum 90 days following NRA approval (per roadmap)	Ongoing – earliest obtained 39 days following NRA approval

CASE STUDY
THE CMC STORY

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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

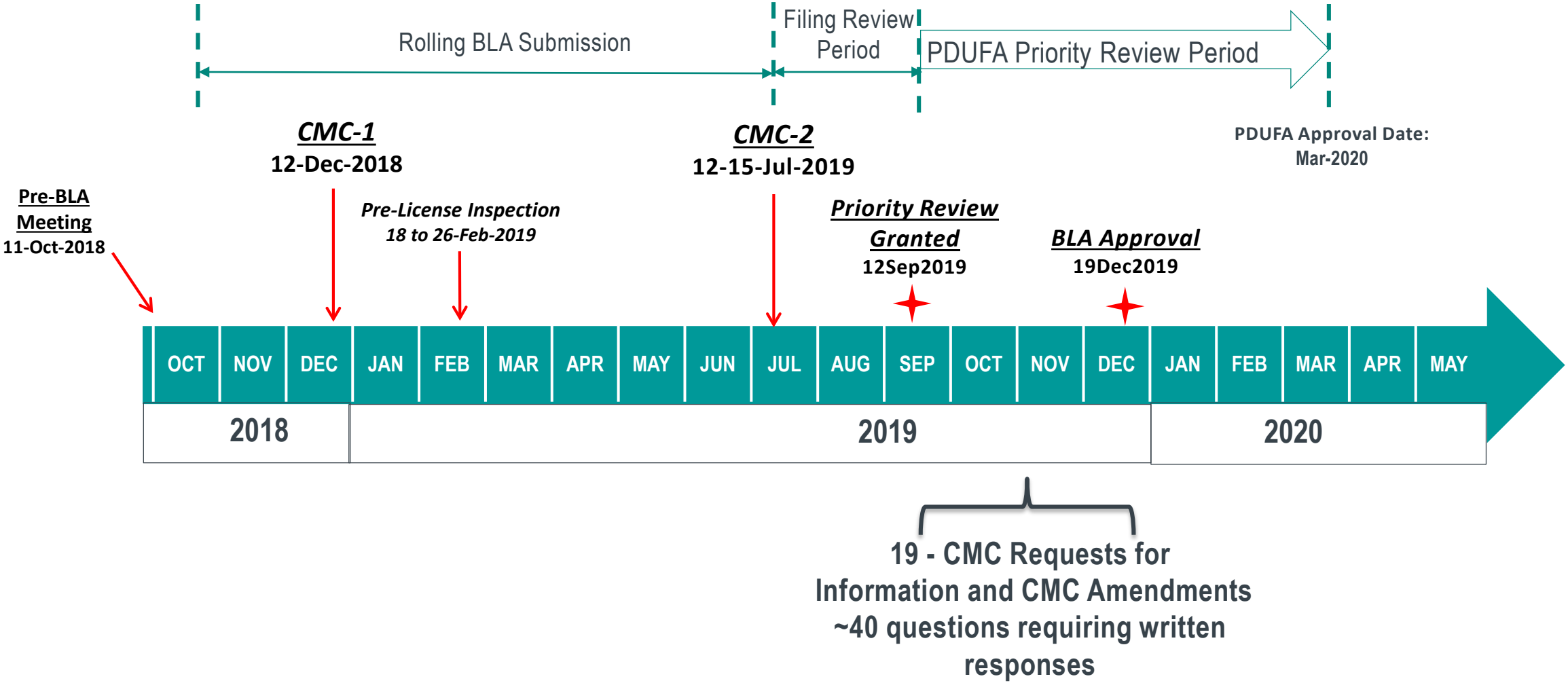
What Happened – Agency Interactions

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

Year	FDA	EMA/WHO
2015	3	2
2016	1	2
2017	1	2
2018	2	2
2019	4	4

What Happened – FDA Submission Timetable



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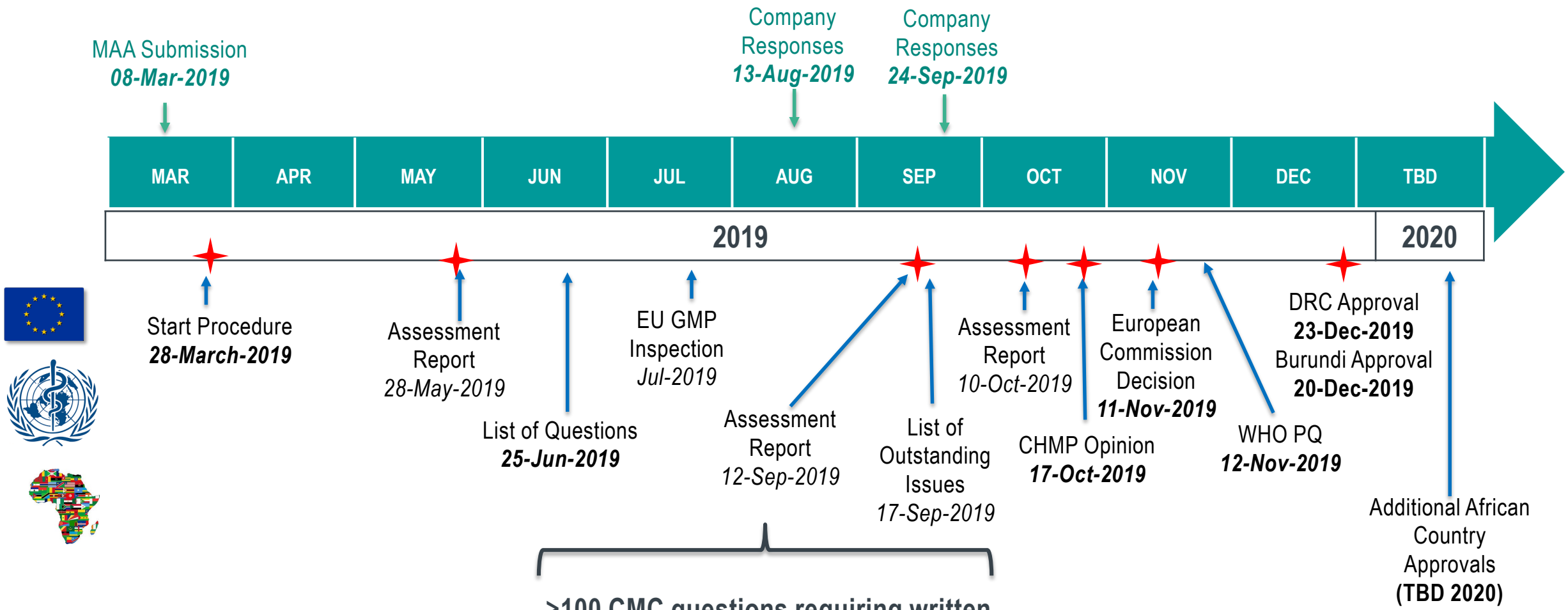
What Happened – EMA (and WHO) Submission Timetable



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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

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THANK YOU

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