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Randi Saunders
Merck & Co, USA, randi.saunders@merck.com

Joseph P Califano
Merck & Co, USA

Dusan Ruzic
Merck & Co, USA

Kristin Valente
Merck & Co, USA

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A VACCINE FOR EBOLA VIRUS – APPROACHES AND RESULTS OF ACCELERATED PROCESS DEVELOPMENT AND CHARACTERIZATION STUDIES

Randi Saunders, PhD; Joseph P Califano, PhD; Dusan Ruzic; Risat Jannat, PhD; Kristin Valente, PhD

Global Vaccines Biologics Commercialization, MMD

Outline

- Ebola Virus
  - Outbreak and Disease
  - Cost of Epidemic
- Vaccine Candidate
  - Development at Merck
  - Strategies to Expedite Development and Characterization
  - Results
- Conclusions

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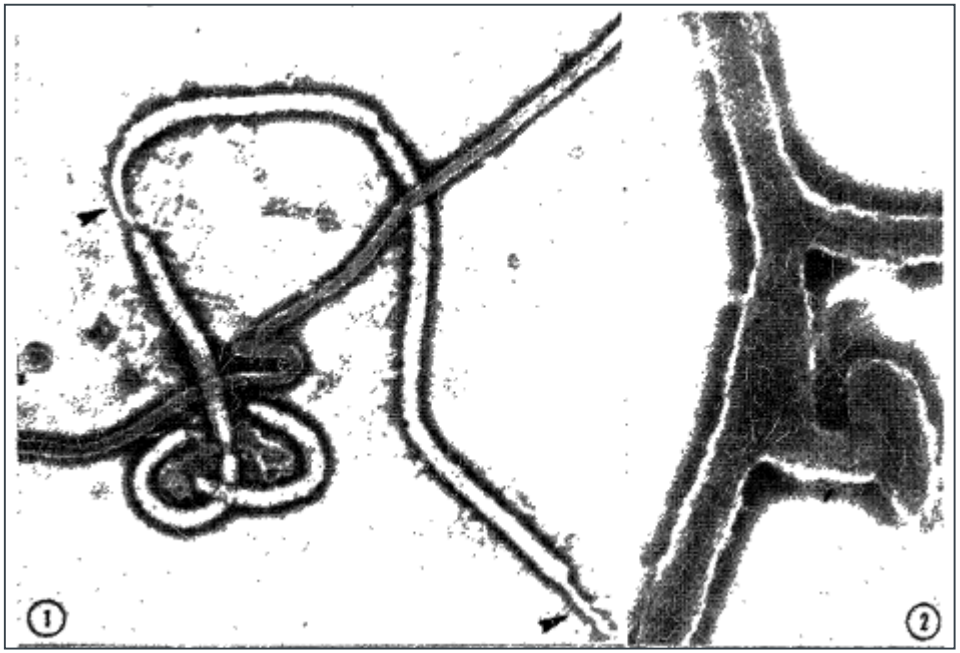
Ebola Virus



Lancet 1977 309(8011):569-571

- Discovered in 1976 near the Ebola River in the Democratic Republic of the Congo
- Causes hemorrhagic fever; severe headache, muscle pain, weakness, fatigue, diarrhea, vomiting, abdominal pain, bleeding/bruising
- Spread through direct contact with body fluids of infected humans/animals
- Bats are a likely reservoir of disease

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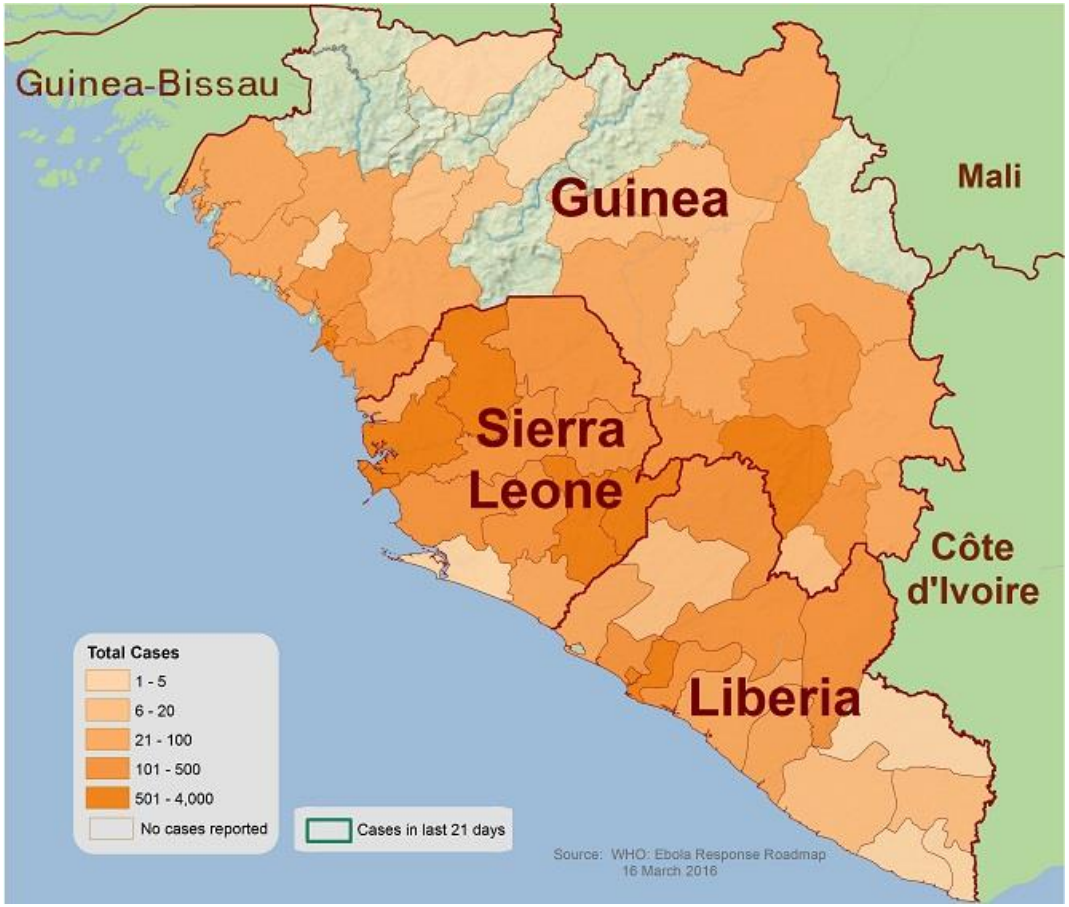
2014-2016 Outbreak



28,616 Total Cases Reported in Guinea, Liberia, and Sierra Leone with 11,310 Deaths as of 27Mar2016 (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"

https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/distribution-map.html

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2014 – 2016 Outbreak

https://www.cdc.gov/vhf/ebola/pdf/impact-ebola-economy.pdf

>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

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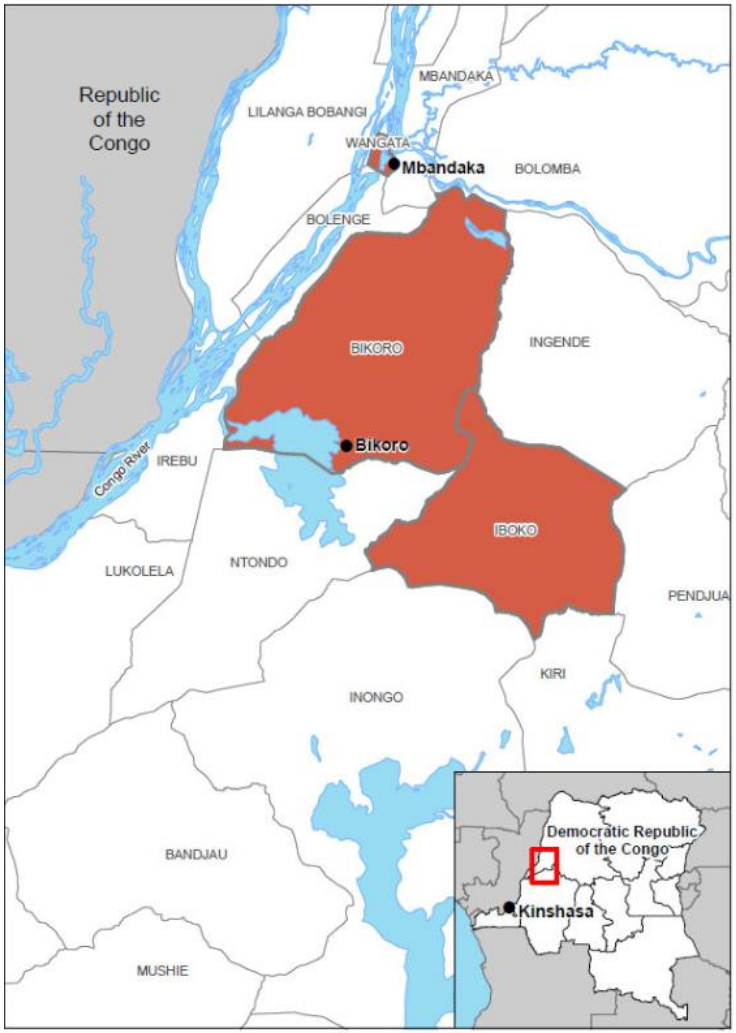
2018 Outbreak



Ebola cases occurred in 2017 and a new outbreak started in 2018.

Latest numbers as of 7 June 2018

Confirmed cases: 38
Probable cases: 14
Suspect cases: 7
Total cases: 59 (including 27 deaths)

http://www.who.int/ebola/situation-reports/drc-2018/en/

World Health Organization:
"Vaccination will be the key to controlling this outbreak" Dr. Tedros Adhanom Ghebreyesus, WHO Director General

https://www.cdc.gov/vhf/ebola/outbreaks/drc/drc-map.html

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The Vaccine Candidate: rVSVΔG-ZEBOV-GP (V920)

https://www.popsci.com/best-of-whats-new-2015/healthcare

- A vaccine candidate was developed
  - Clinical studies were a global effort – supported by many countries and health agencies
  - Results from a ring vaccination trial suggests the V920 vaccine has high protective efficacy and effectiveness
- The vaccine was in-licensed by Merck who took on the responsibility for research, development, and manufacturing efforts

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V920 Development at Merck

On Nov 24th 2014 Merck announced an exclusive worldwide agreement with NewLink Genetics to research, develop, manufacture, distribute, and license V920, an investigational vaccine candidate. Merck began work on V920 in 2015

- **Process Development Scope and Goals**:
  - Process scale-up in support of Emergency Use and commercial dose production
    - Increase lot size from clinical manufacturing scale
    - Show comparability between clinical and commercial scale
  - Process development and characterization to fully define a robust manufacturing process
    - Generate lab-scale data to support process parameter ranges
    - Define the Final Manufacturing Process (FMP) Description
- **New approaches were needed to accelerate development and characterization work**
  1. Work in parallel
  2. Use a risk-based approach to prioritize development studies
  3. Create and use a scale-down model to increase experiment throughput
  4. Consider single-use solutions

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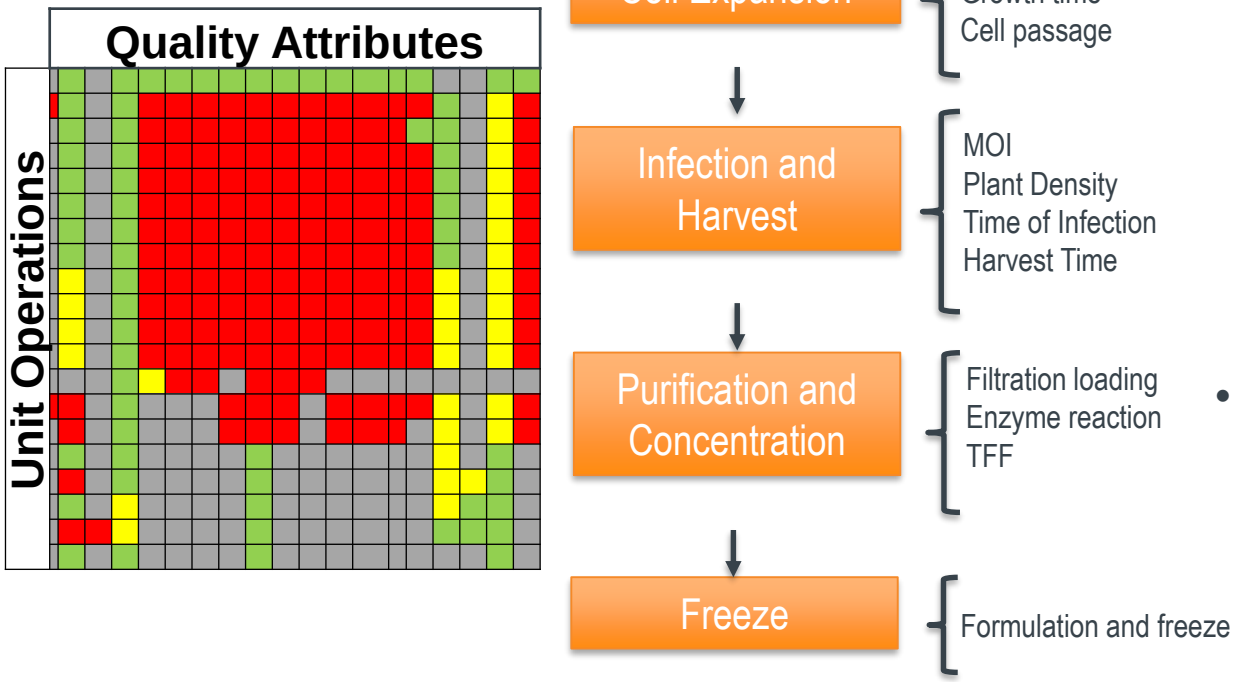
V920 Development at Merck

Approach 1: Work in Parallel

- Team 1: Scale-up and emergency use production
- Team 2: Process Development and FMP definition

Approach 2: Use a Risk-Based Approach to Prioritize Experiments; Leverage Existing 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

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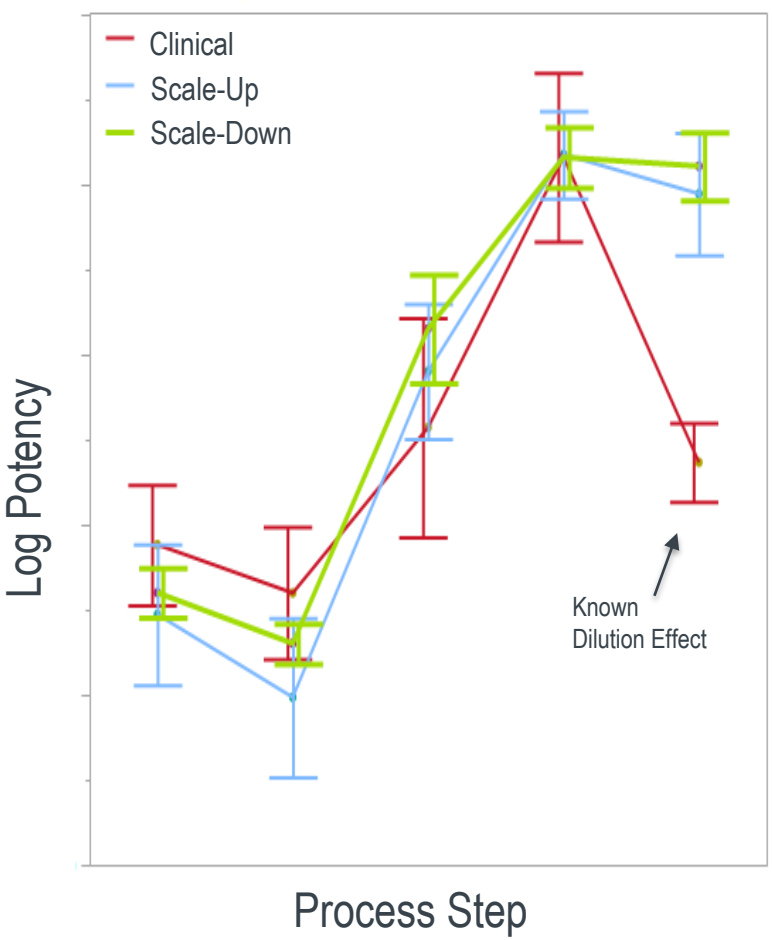
V920 Development at Merck

Approach 3: Develop a Scale-Down Model for experimental work



- Reduced cycle time to generate data
  - Reduced from 8+ weeks to 3 weeks
- Reduced purification process volume from 80L to 1L to enable design of experiments
  - Infection – cell/virus interactions
  - Purification – enzyme reaction interactions
- Demonstrated comparable to full-scale and clinical batches

By the Numbers

- 450+ vials of cells used for lab-scale experiments
- 200+ experiment notebooks generated and reviewed
- First draft of FMP issued within 1 year of project start

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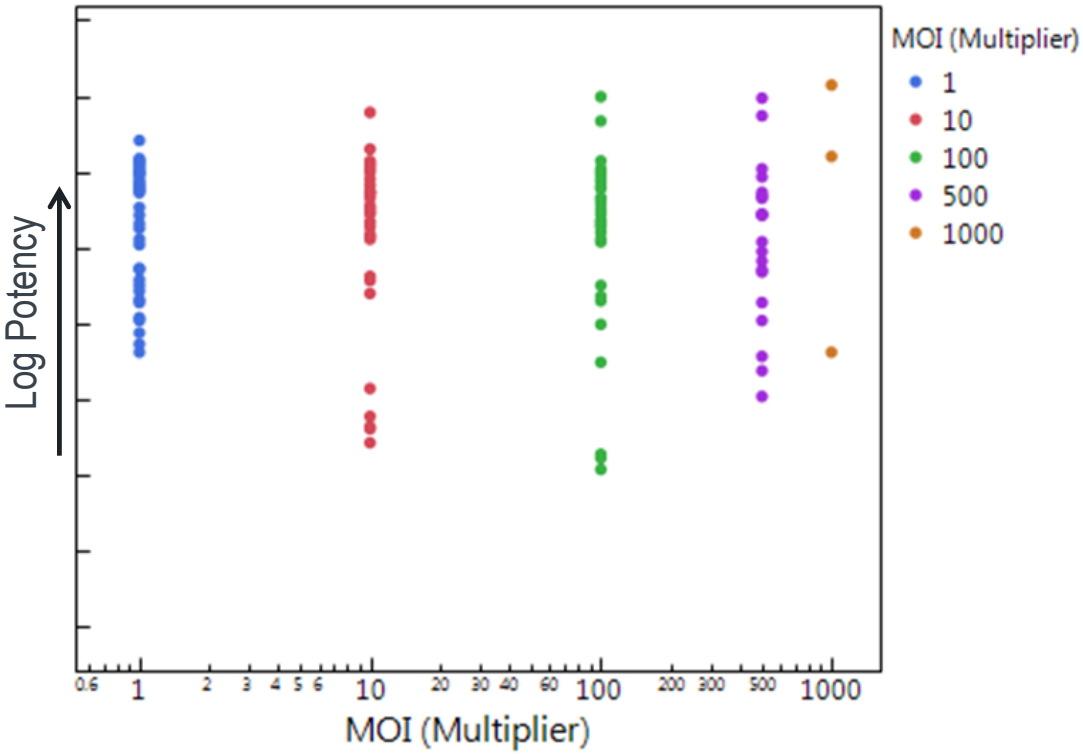
V920 Development at Merck

Multiplicity of Infection (MOI) Robustness



- MOI typically a very sensitive parameter for infection
- Within our target harvest window a 1000x MOI range is capable of producing drug substance bulks with the same range of potencies
- Results in a very robust process and design space

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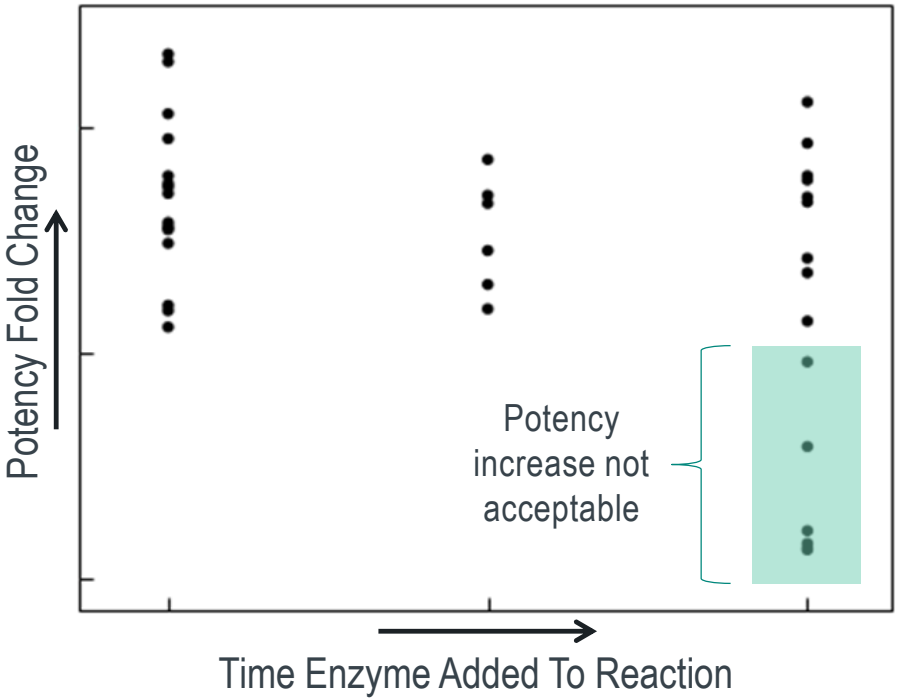
V920 Development at Merck

Purification Robustness



- Multifactor DOE performed looking at enzyme reaction parameters
- Only the time that the enzyme was added to reaction was found to be statistically significant to achieve the desired potency increase
  - Failure point used to set PAR
- Tangential Flow Filtration capable of robustly clearing process residuals with no critical process parameters

PAR, proven acceptable range

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V920 Development at Merck

Approach 4: Develop a Single-Use Drug Substance Process

- Desire for modular single-use components with sterile connectors

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

Layout Study

- Evaluate designs – obtain VOC, to support component design simultaneously with operations staff onboarding and facility retrofit
- Hands-on training and team building
- Assembly layout for process and area fit
- Began to understand waste streams

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

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V920 Development at Merck

Approach 4: Develop a Single-Use Drug Substance Process

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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

- 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)

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

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Conclusions

Several approaches were used to expedite process development and characterization of the V920 vaccine candidate and develop a robust process:

1. Work in parallel
2. Use a risk-based approach to prioritize development studies
3. Create and use a scale-down model to increase experiment throughput
4. Robust Process Results from experiments
    1. A 1000x MOI range produces acceptable potencies
    2. Enzyme addition is critical for achieving expected potency increase during purification
    3. TFF robustly clears process residuals
5. Consider single-use solutions

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- V920 Product Development Team
- Burgwedel Biotech GmbH

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