EMA /US FDA Workshop on

support to quality development in early access approaches

Ebola Vaccine Case Study for Session 5a BIOLOGICALS (PROCESS VALIDATION AND CONTROL STRATEGY)

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Bio Biotechnology Innovation Organization

ebe european biopharmaceutical enterprises

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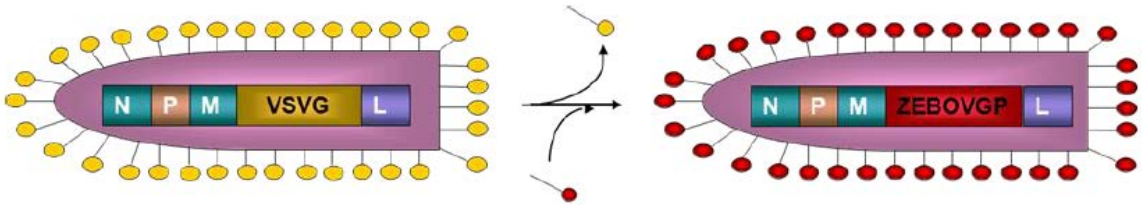
Vaccines Europe An industry for healthy lives

V920 (rVSVΔG-ZEBOV-GP): An Ebola Vaccine

- Product information: V920 is an investigational recombinant, replication-competent, vesicular stomatitis virus (VSV)-vectored-vaccine containing the glycoprotein of Zaire ebolavirus (ZEBOV)
- The Vaccine Candidate: rVSVΔG-ZEBOV-GP rVSV expressing envelope GP of the Zaire Ebola virus species (Kikwit variant)



VSV Wild Type | Glycoproteins switched | VSVΔG/ZEBOV-GP

Key:
N= Nucleoprotein
P=Phosphoprotein
M=Matrix
G= Glycoprotein
L= Polymerase

- Development stage: Phase 3
- Product class: Vaccine
- Geographical region: Clinical trials were conducted in Africa, North America and Europe
- Sponsor/applicant profile: MSD is a global healthcare company
- Milestone: PRIME status (EMA) and Breakthrough Therapy designation (US FDA)- granted to rVSVΔG-ZEBOV-GP) June 2016

Rapid Product Development Challenges

- Clinical development program was conducted very rapidly, with twelve Phase 1, 2, and 3 trials ongoing during the 2014-2016 Ebola outbreak.
- Clinical lots were made at a contract manufacturing organization (CMO) and clinical consistency evaluation was performed using lots made at a Biological Pilot Plant prior to scale up of the process and transfer to the final manufacturing facility

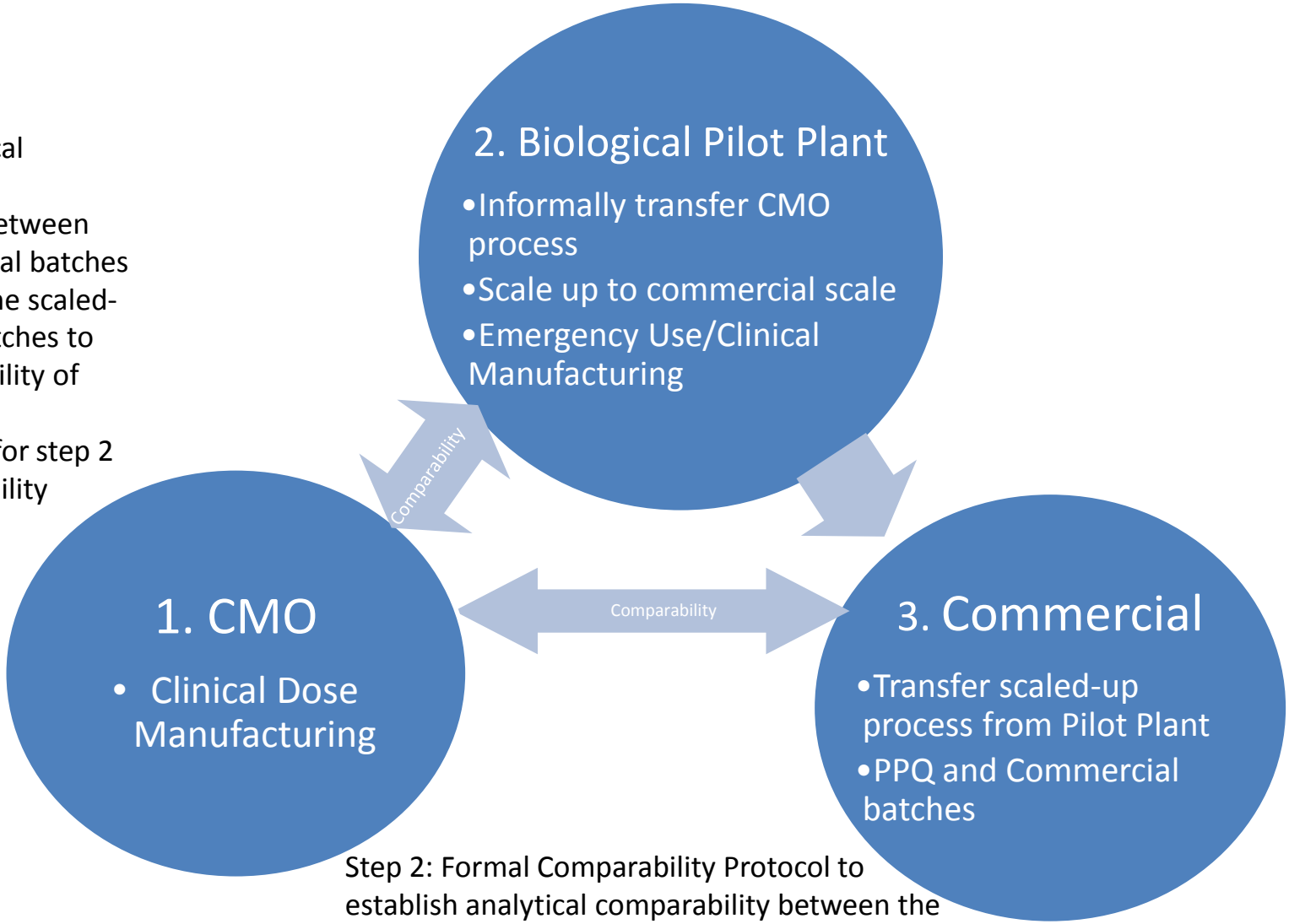
CMC Approaches to Accelerate Product Development

- **Use of clinical formulation:** Limited optimization to avoid formulation development delays
- **Analytical comparability approaches:** Transfer of the clinical scale process to a Biological Pilot Plant (BPP) where process scale up occurred and additional vaccine supplies were produced for clinical trials and emergency use; analytical data showed that material manufactured at the CMO and the BPP are comparable demonstrating that the process could be transferred and supporting the use of an analytical bridging approach for the final manufacturing facility
- **Tailored validation package:** occurred in parallel at the final manufacturing facility
- **Advanced submission of CMC data:**

- In the EU an analytical comparability protocol was submitted to define proactively the data to be supplied during the MAA review;
- In the US data will be submitted under the BLA on a rolling basis with a pre-defined start of the review process to be determined by the FDA

Analytical Comparability Approach

Step 1:
Establish analytical comparability *retrospectively* between the original clinical batches from CMO and the scaled-up Pilot Plant batches to determine feasibility of scale up and set prospective A/C for step 2 formal comparability



Step 2: Formal Comparability Protocol to establish analytical comparability between the PPQ batches at the commercial site and the original clinical batches from the CMO

Parallel Validation Activities

Parallel Drug Substance and Drug Product Validation Activities:

Drug Product validation activities will commence prior to the completion of Drug Substance validation

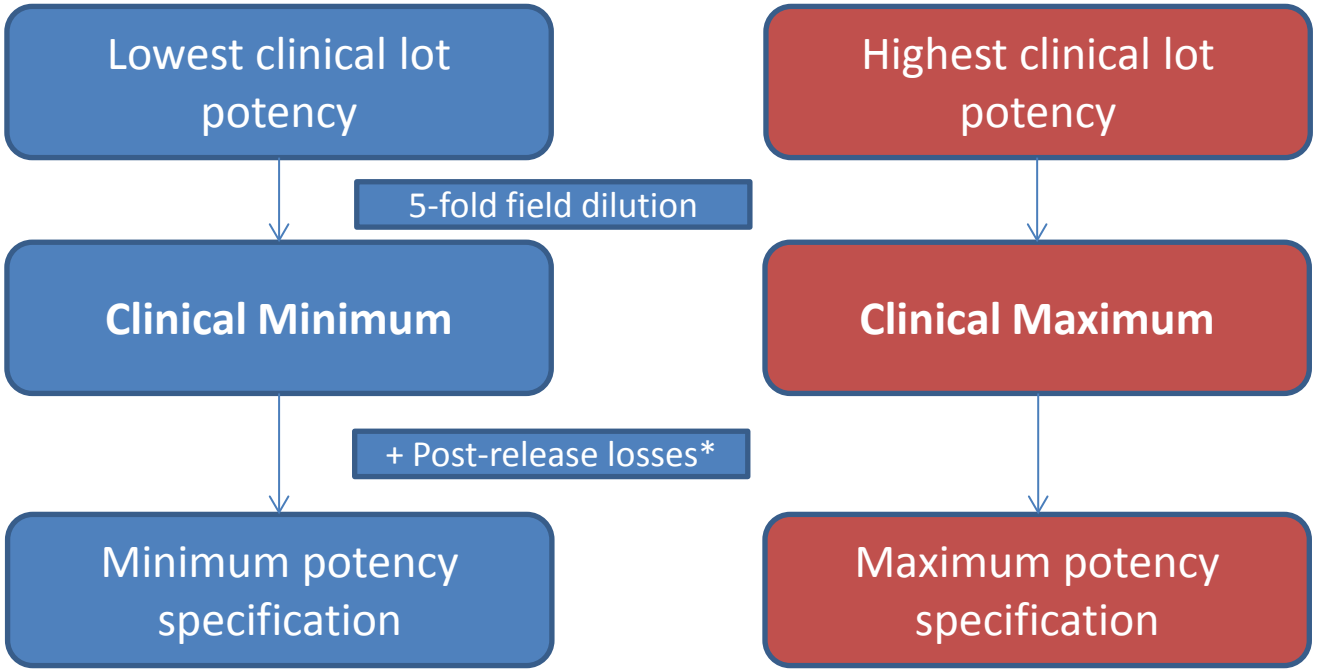
Advanced Submission of CMC data:

Submission of CMC data on a rolling basis are being discussed with both EMA and FDA through informal and formal meetings in order to provide sufficient information for the agencies to review prior to conducting facility inspections while validation activities are in the process of being completed. The amount of CMC data and timing for submission will be determined after discussion with both agencies including:

- DS PPQ and DS comparability data required to start the review clock
- DS and DP PPQ data required for approval
- Timing of submission of each DS and DP PPQ data set: initial submission, during review and post-approval stages
- FDA GMP Inspection timing to coincide with DS and DP PPQ manufacturing taking place

Clinically Relevant Control Strategy

Derivation of the commercial drug product potency (PFU/mL)

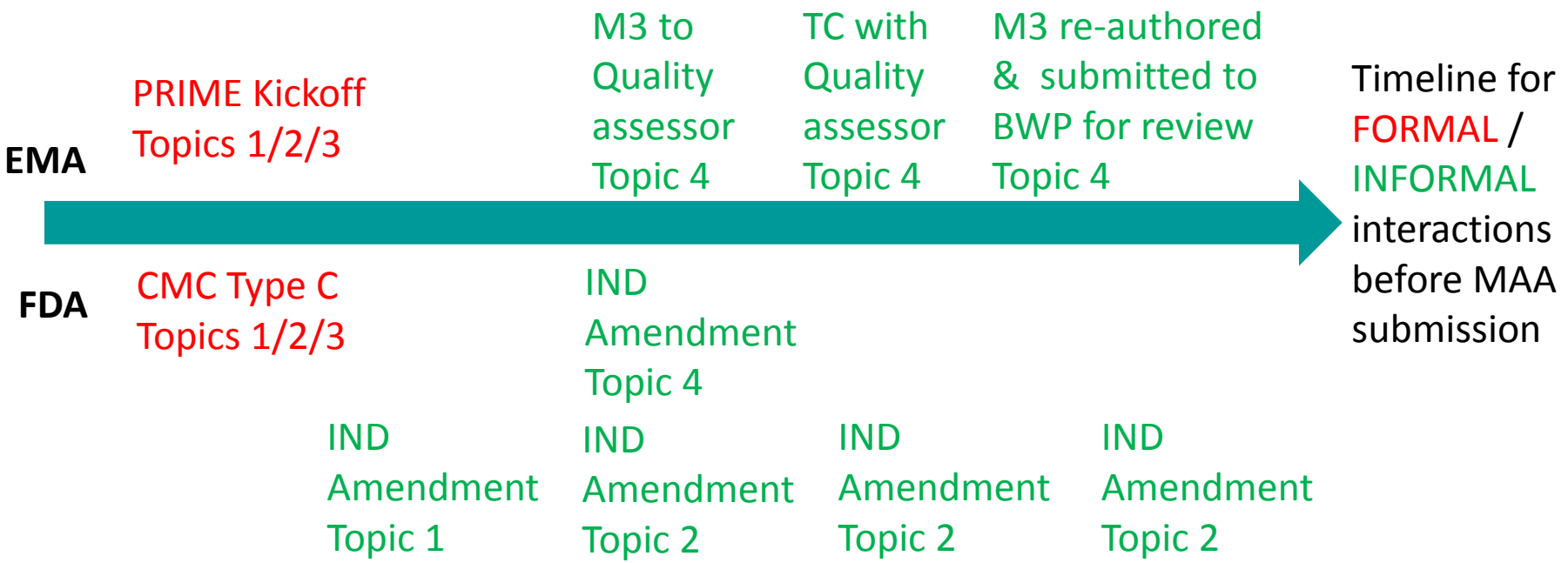


*Time at 2-8 °C and time at 25°C

Frequent Interactions on CMC Topics before MAA submission

CMC topics discussed formally and informally with FDA and EMA prior to submission of license application including topics:

1. Analytical method validation for key methods impacting DS and DP
2. Adventitious Agent control strategy
3. Commercial tests and specifications
4. Review of draft M3 section on key CMC topics ***identified late*** that could impact approval



Summary

- Frequent informal and formal discussions with EMA and FDA under PRIME and BT has facilitated development of an Ebola vaccine.
- Transparent and open communications between the company and both agencies and review of the advanced CMC data submissions allowed the continued progress of the project, limiting the potential risk to submission of the Marketing Application by enabling alignment with regulator's expectations.
- Feedback on key aspects of the control strategy and comparability protocol including setting of acceptance criteria and setting clinically relevant specifications through expedited Agency interactions have enabled the company to focus on the remaining items that are needed to complete the dossier.
- Comparability protocols were discussed under the IND by CBER/FDA and in the EU under the PRIME Scheme.

Acknowledgements

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