MERCK'S APPROACHES AND CHALLENGES FOR IMPLEMENTATION OF PHASE-APPROPRIATE GMP CONTINUUM

CASSS CMC Strategy Forum

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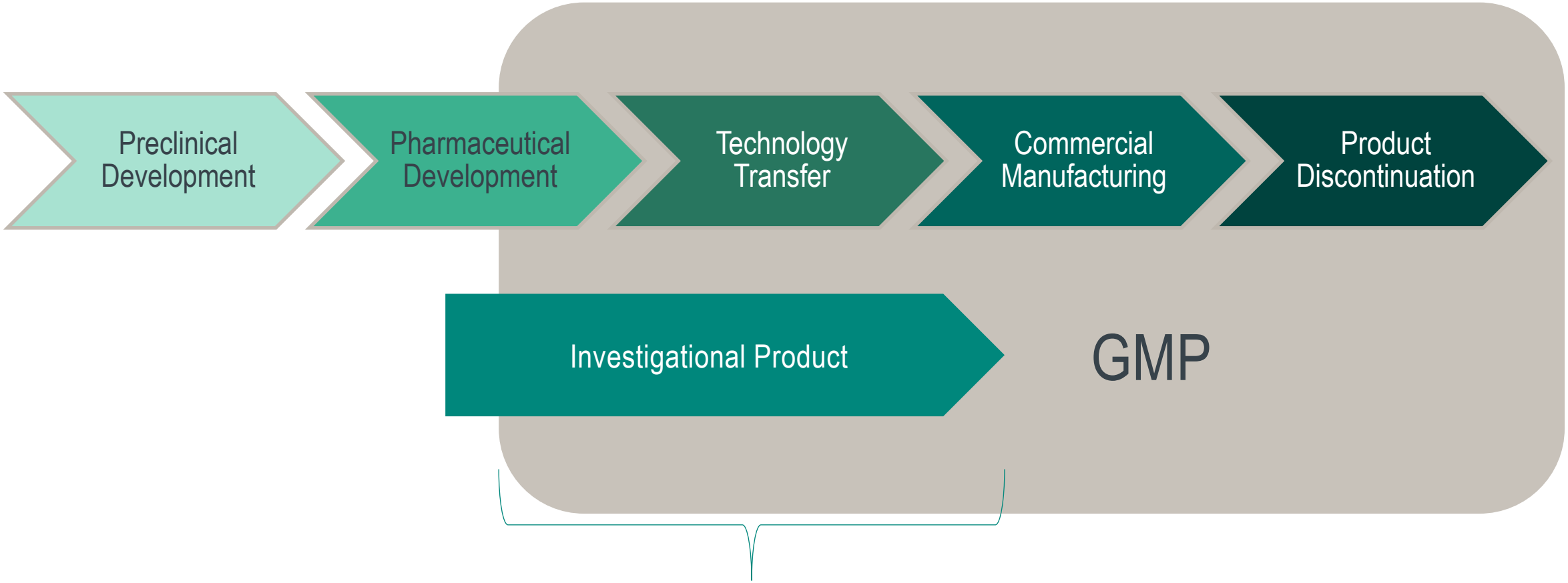
15 Oct, 2020

Overview

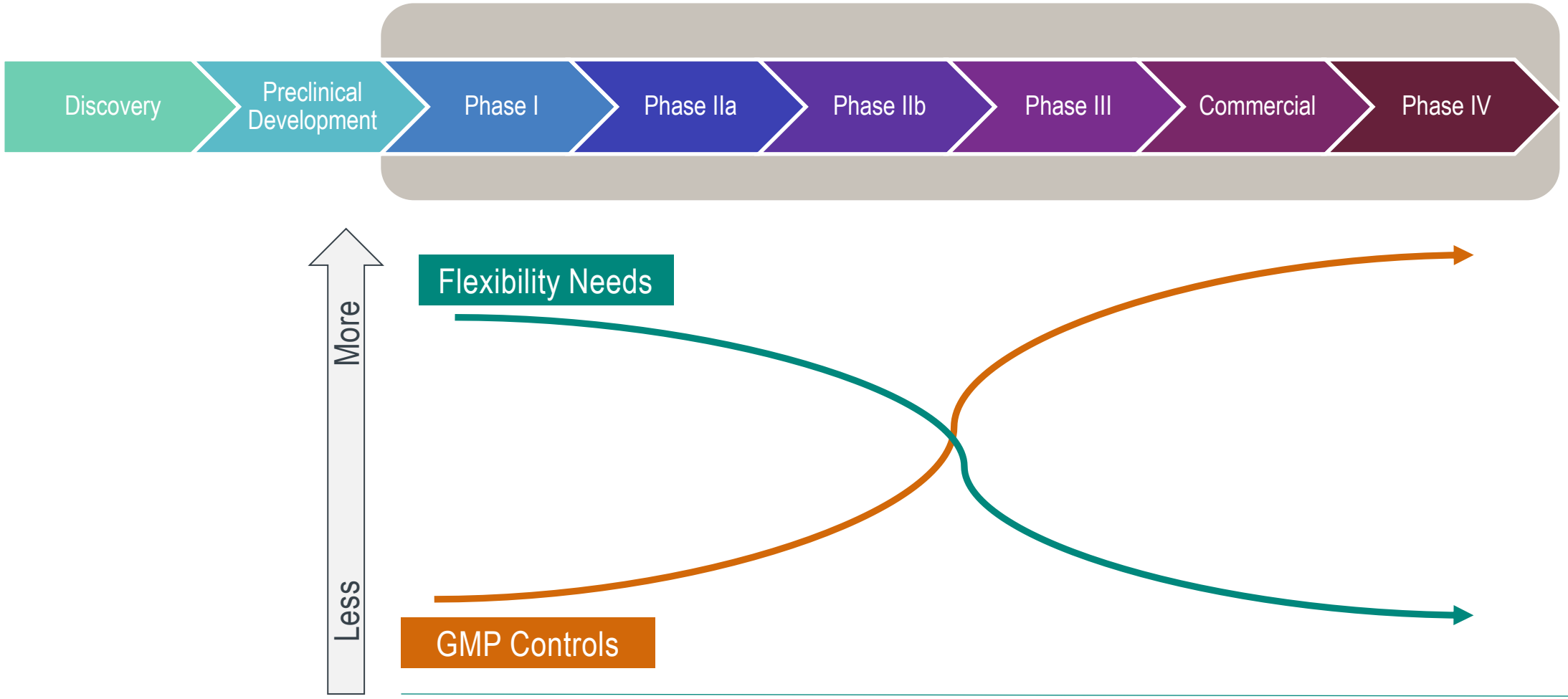
- The Merck Development Continuum
- The Challenges of bringing an Ebola Vaccine to our patients
- Other Considerations

ICH Q10 Pharmaceutical Quality System

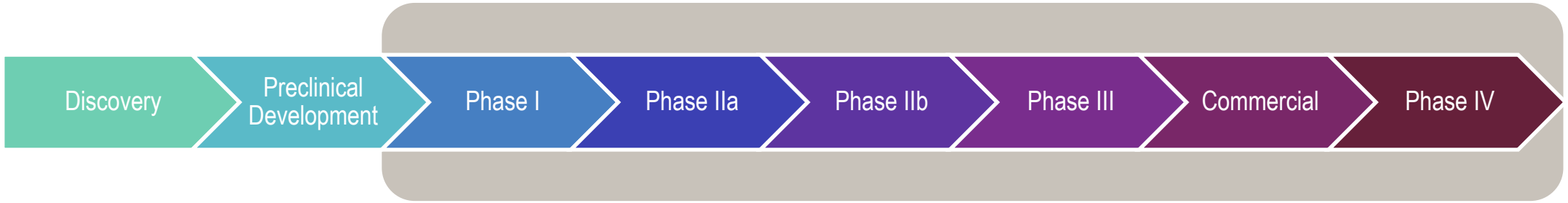


What is a GMP Continuum?

GMP requirements appropriate to the Phase of Pharmaceutical Product Development



Examples of a GMP Continuum



Cleaning Verification
- No terminal Sterilization required

Raw Materials
- Qualified

Analytical
- Reduced validation requirements

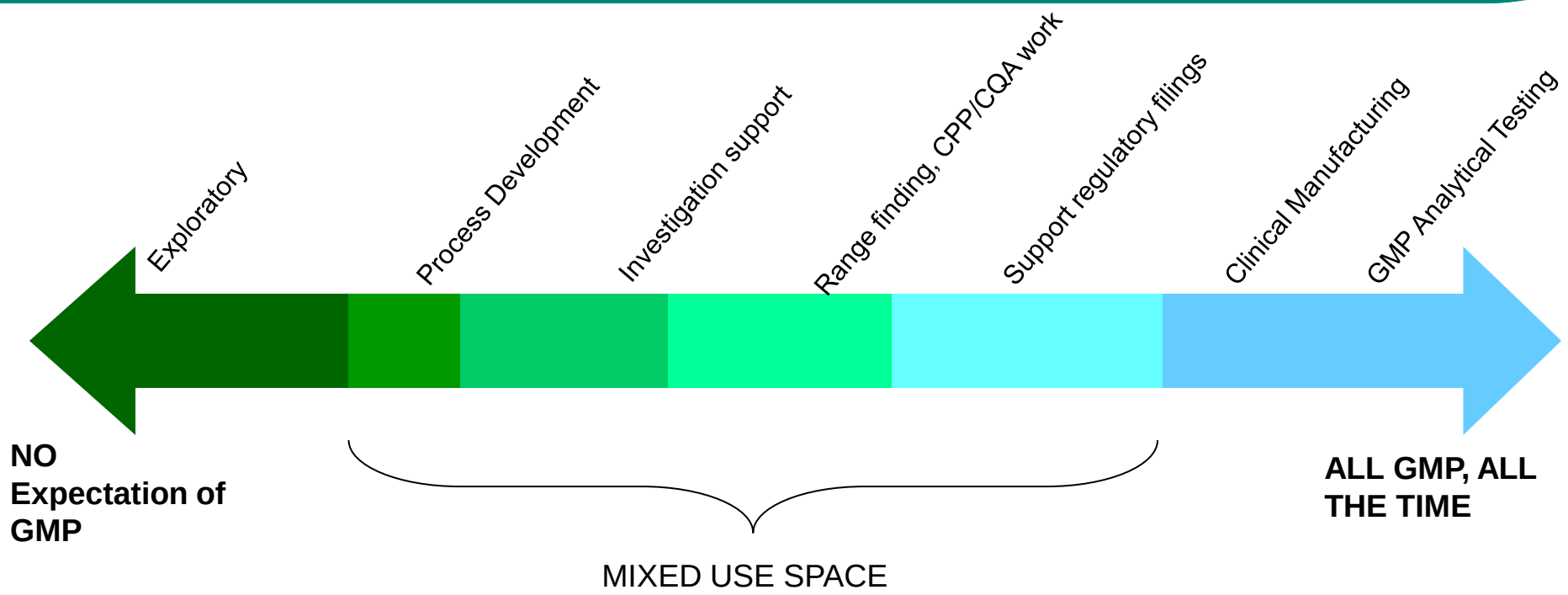
Cleaning Validation
- Terminal sterilization required where possible

Raw Materials
- Validated/Audited

Analytical:
- Full validation requirements

EM, Risk Mgmt, Calibration, Change Mgmt, Deviation Mgmt, Document Mgmt

Introduction: GMP Continuum

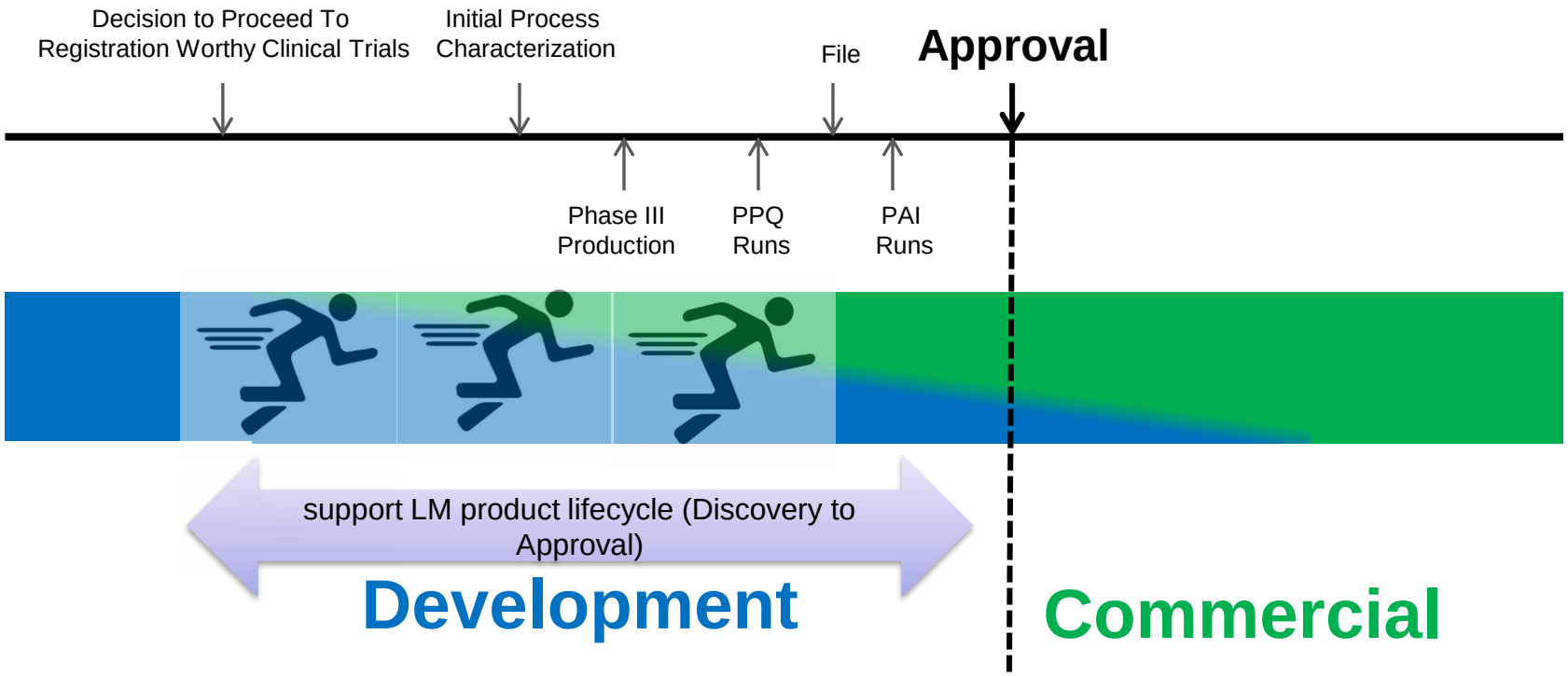


Calibrate GMP Oversight and Control Based on Work Performed

What's on the GMP Continuum?

- Release & Stability testing, In-Process testing
- Technical Data as part of characterization, e.g. comparability data.
- Data used within int/ext inspections, e.g. validation reports, comparability reports.

Driver for Change



Timelines are faster, activity is the same. How to enable LM programs for speed to patient?

Build a positive quality culture and align on quality principles in the DEVELOPMENT space

Analytical Approaches – Large Molecule

	Phase 1	Phase 2	Phase 3	FSS	PPQ	Com.
Potency	Qualified	Qualified	Validated	Validated	Validated	Validated
GMP-Release & Stability	Qualified	Qualified	Qualified	Validated	Validated	Validated
In-Process Control (IPC)	Qualified	Qualified	Qualified	N/A	Validated	Validated
Characterization of DS or DP (on GMP Material)	Scientifically Sound	Scientifically Sound	Qualified	Qualified	Qualified	Qualified
Characterization of Impurities	Scientifically Sound	Scientifically Sound	Scientifically Sound	N/A	N/A	N/A
In-Process Intermediate Characterization (IPIC)	Scientifically Sound	Scientifically Sound	Scientifically Sound	N/A	Qual	Qual
Comparability	N/A	Scientifically Sound	Pre-Qual	N/A	Qual	Qual
Process Characterization (Range Finding)	Pre-Qual	Pre-Qual	Pre-Qual	N/A	Pre-Qual	Pre-Qual

Scientifically Sound: Uses SME assessment for appropriateness of method. No assessment per ICHQ2(R1)

Pre-Qualification: Limited Assessment via ICH Q2(R1) expectations. "Fit-for-use"

Qualification: Assessment via ICH Q2(R1), but less robust than a validation

Validation: Full Assessment of All Criteria in ICH Q2(R1) with a strong sample size. Robustness studies should be completed in conjunction with the formal validation studies (but typically a separate activity)

Potency always has the most discussion due to the time it takes to validate the method. It is our common practice to validate for phase 3, for some of our accelerated programs we would consider to have the potency assay Qualified and Validated prior to PPQ.

Formal Stability Studies (FSS) – for 2 products we used qualified methods for FSS and perform a gap analysis once they were validated. This allowed FSS to begin earlier to obtain more shelf-life data for an accelerated BLA filing.

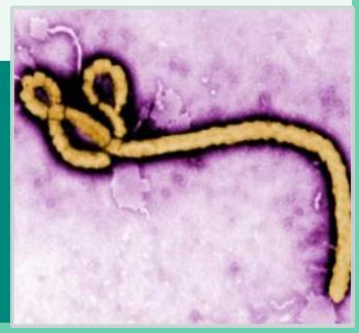
Delivering the Ebola Vaccine(ERVEBO©) Rapidly in Emergency Outbreak

Situation

- Ebola Zaire virus outbreak (2014-2016) caused 11,000+ deaths & recent Dem. Republic of Congo outbreak caused 1000+
- Outbreaks are **unplanned** and **unexpected**
- Containment is **VITAL**

Expectation

- V920 (frozen, live attenuated rVSV vaccine) is proving to be **100% effective** as a pre-exposure prophylaxis
- Merck needs to "**stand ready**" to supply potentially life-saving vaccine



Partnership

- **Collaborate** with global & national health organizations to develop, fund and deliver V920 vaccine to emergency situations
- **Partnership, Communication and Commitment** is **CRUCIAL!**

World Health Organization · CDC · National Institutes of Health · BARDA · Médecins Sans Frontières

Positioning Merck to Quickly Respond When Every Minute Counts

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Repeated Ebola Outbreaks in DRC: Investigational Vaccine Doses Administered to >340,000 Individuals as Part of Outbreak Response

May 8-July 24, 2018 – Equateur Province

GLOBAL HEALTH

Ebola Outbreak in Congo Has Ended, W.H.O. Says

The outbreak, the first in which a new vaccine was quickly rolled out, was extinguished in less than three months, with 33 deaths.

By Donald G. McNeil Jr.

July 24, 2018

Special communication of the Minister of Health regarding the evolution of the ninth Ebola outbreak in DRC

The use of vaccination in this Ebola response has been a game-changer as it allowed us to break the chain of transmission and contain the virus more quickly. Since the beginning of the vaccination microplan on May 21st, 3,330 people have

August 1, 2018- June 25, 2020 – North Kivu and Ituri Provinces

HEALTH NEWS AUGUST 1, 2018 / 10:32 AM / 20 DAYS AGO

Congo declares new Ebola outbreak in eastern province

Fiston Mahamba

TIME WORLD • CONGO

Congo's Ebola Outbreak Is Now the Second Largest in History, WHO Says

June 1, 2020-ongoing – Equateur Province

New Ebola outbreak detected in northwest Democratic Republic of the Congo; WHO surge team supporting the response

World Health Organization REGIONAL OFFICE FOR Africa

Ebola outbreak in western Democratic Republic of the Congo reaches 100 cases

Brazzaville, 21 August 2020 The number of cases in the ongoing Ebola outbreak in western Democratic Republic of the Congo (DRC) has reached 100, a near two-fold increase in a little over five weeks.

Risk Management Approaches to Accelerate Development

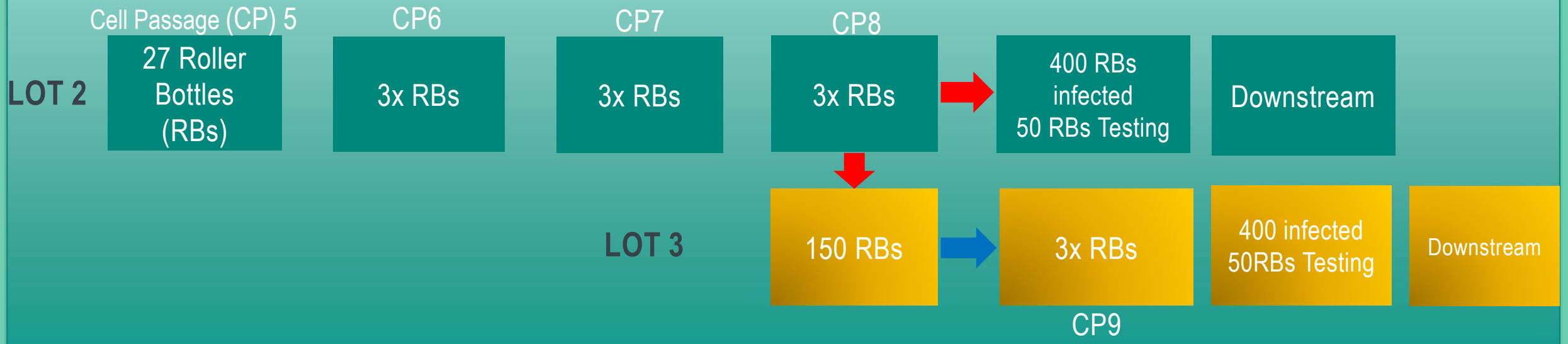
- Use of risk matrices in early phases to support setting of specifications, stability requirements, cleaning validation, container closure validation and matrix qualification for bioburden/sterility testing.

  - Example Ebola vaccine: Since the process is aseptic, we performed a risk assessment to justify that upstream process simulations were not required in Phase I since we had full data to support that the cell passages were maintained long enough that we would see any contaminants and under conditions where contaminants could grow if present

Drug Substance Challenges and Approaches to Overcome

Merck targeted manufacturing additional lots of Drug Substance in 2019 to augment supplies to support outbreak response. Lot 1 had to be terminated due to a power outage and with a facility shutdown approaching, it was not possible to start a new lot.

An Innovative Production plan was implemented to keep manufacturing on schedule that leveraged available data which supported use of an additional cell passage:



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FDA Licensure – Flexibility & Collaboration to Speed Approval

- During the pre-BLA meeting, FDA agreed to consider a rolling BLA submission w/ partial CMC modules submitted prior to PPQ lot manufacture.
- The partial CMC modules would contain:
  - DS & DP engineering release & comparability data
  - DS & DP process sims, analytical methods & validation,
  - comparability protocol
  - facility information to support an inspection during PPQ manufacturing
- FDA will need at least 8 weeks to review the CMC sections before coming onsite for an inspection
- They would observe DS & DP PPQ manufacturing during their inspection
- Approved PPQ reports will be needed to complete the rolling BLA submission

Novel Regulatory Strategy to Accelerate Approval in At-Risk Countries

- **Objective**: Obtain approvals in at-risk African countries as quickly as possible, facilitated by WHO Prequalification, and supported by approvals from the European Medicines Agency and U.S. FDA, in order to help meet global preparedness and response objectives.
- **Mechanisms:** Collaborative reviews including EMA, WHO PQ group, AVAREF, and African country NRAs. Active communication with Regulatory Agencies and between Regulatory Agencies including real-time information sharing facilitated by Breakthrough Therapy and Priority Medicines Designations. Use of rolling submissions to support accelerated assessments.

Areas of Focus

EMA Conditional Approval 11Nov2019	FDA Licensure 19Dec2019	WHO PreQualification 12Nov2019	Licensure in 6 countries as of Sep2020

Other Considerations that can facilitate speed to filing

- Process and Analytical Platform approaches
- Continuous Processing
- Automated Systems & Data Management
  - Electronic Batch Records facilitates Quality review by exception
- Implement Facility and process contamination controls in Early Manufacturing
- Single Use components – reduce cleaning validation but add leachable & extractable studies
- Minimize Outsourcing activities
- Facilities of the future – flexible, modular design and can be easily relocated.
- Expedited regulatory pathways, such as Breakthrough Therapy Designation and Priority Medicines (PRIME) status, can accelerate development

WORK SMARTER, NOT JUST FASTER

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QUESTIONS?

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