Accelerated Development for Biopharmaceutical Products

Josh Grieco

February 5th, 2018

Overview

- Accelerated development drivers
- CMC development considerations
- Case Study – Early Investment in Process Performance Qualification (PPQ) to enable acceleration

Drivers for Accelerated Development

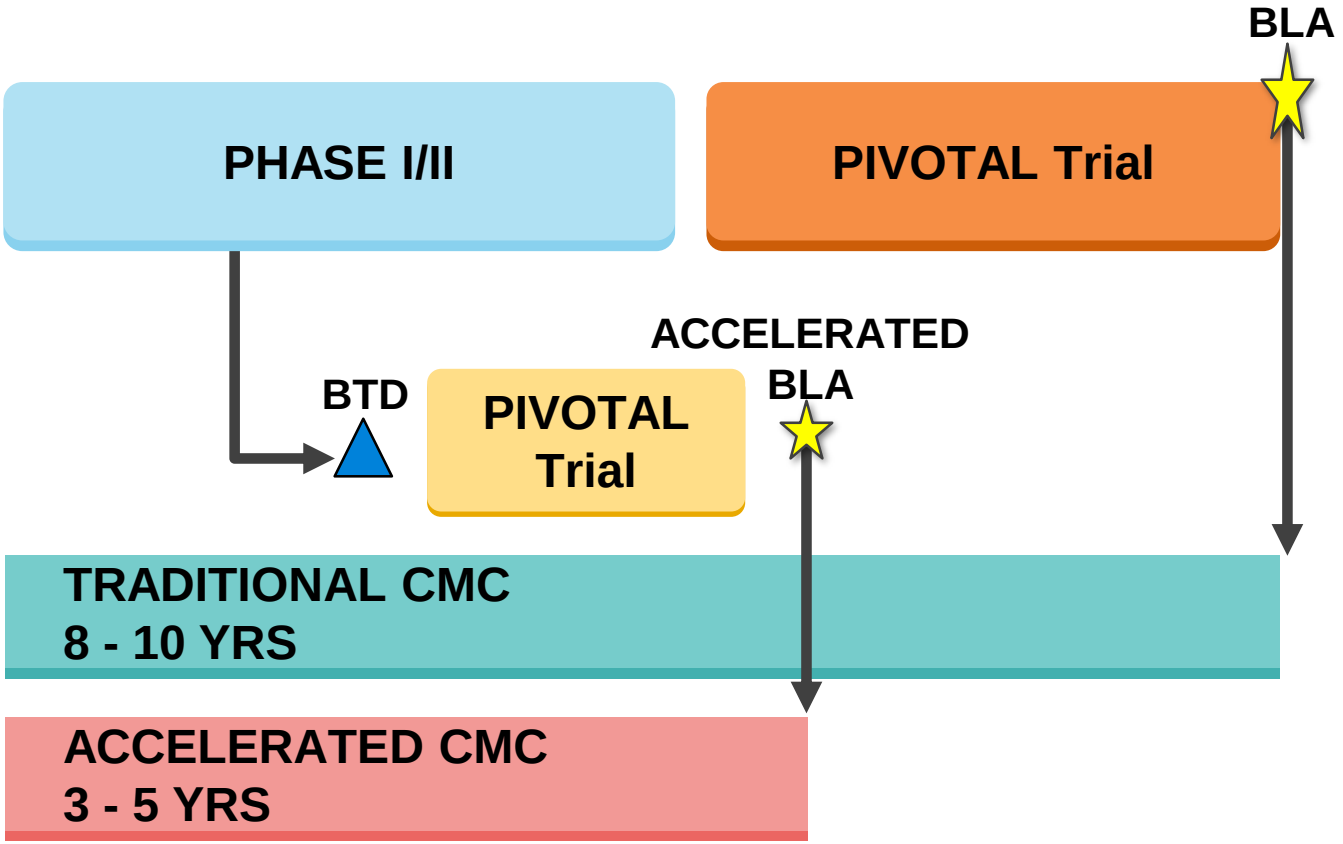
- Scientific advances have enabled better genetic and molecular understanding of certain diseases resulting in opportunities for more rapid clinical development of new medicines.
- Ongoing need for new medicines to treat serious medical conditions with unmet medical need.
- Increasingly competitive environment (oncology, etc.)
- New HA regulatory pathways to expedite development and approval of these innovative medicines.
  - Breakthrough therapy designation (BTD) programs – FDA
  - Adaptive Licensing Pathways and PRIME in Europe
  - Sakigake in Japan

Paradigm Shift in Clinical Development Compress Timelines by Combining Phases

Standard Drug Development Paradigm: 8-10 years

Alternative Development Paradigms: 3-5 years

Accelerated Clinical Programs Compress CMC Development



Activities to enable accelerated CMC development need to be initiated early and typically prior to being granted any formal Health Authority Priority Category

Investment Considerations

- Need to invest early at risk to enable acceleration
- Prioritize molecules
  - Unmet medical need
  - Disease area
  - Evidence of response
- Identify key long lead development activities to initiate early
- Gate additional investment
  - Future clinical readouts
  - Granting of BTD or other priority category by Health Authority
- Reassess portfolio often and as new data becomes available

Key CMC Development Considerations

- Cell Line Development
  - Optimize early and stay with early phase clone
- Formulation Development
  - Early development studies and forward looking dosage considerations
- Method Development (cell based potency, etc.)
  - Develop robust assays (or leverage platform) early
- Critical Quality Attributes (CQAs) and Control System
  - Early assessment of CQAs
  - Leverage early phase control system

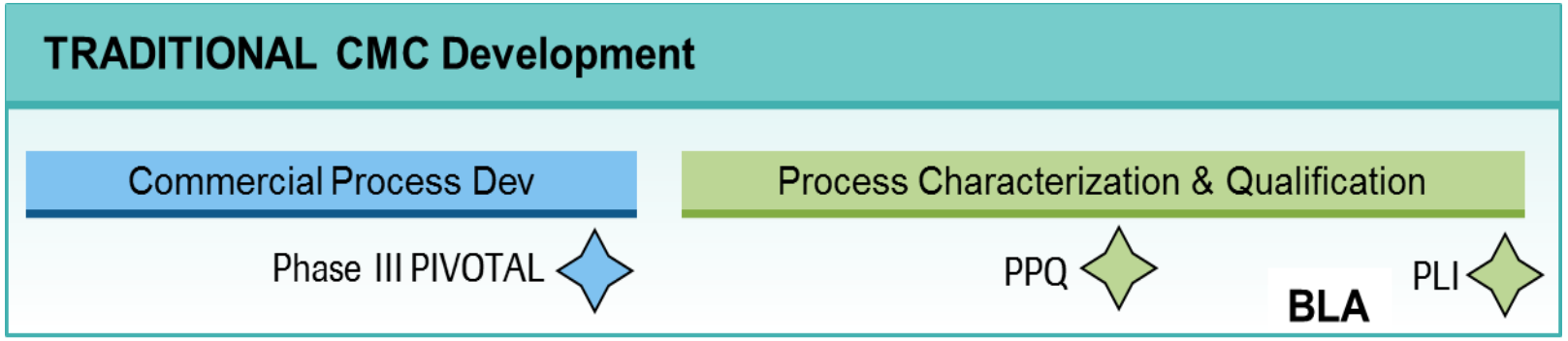
Accelerated CMC Development Case Study

Registration Enabling Campaign

- **Early Investment in Process Performance Qualification (PPQ) to enable acceleration**

Process Performance Qualification PPQ Overview

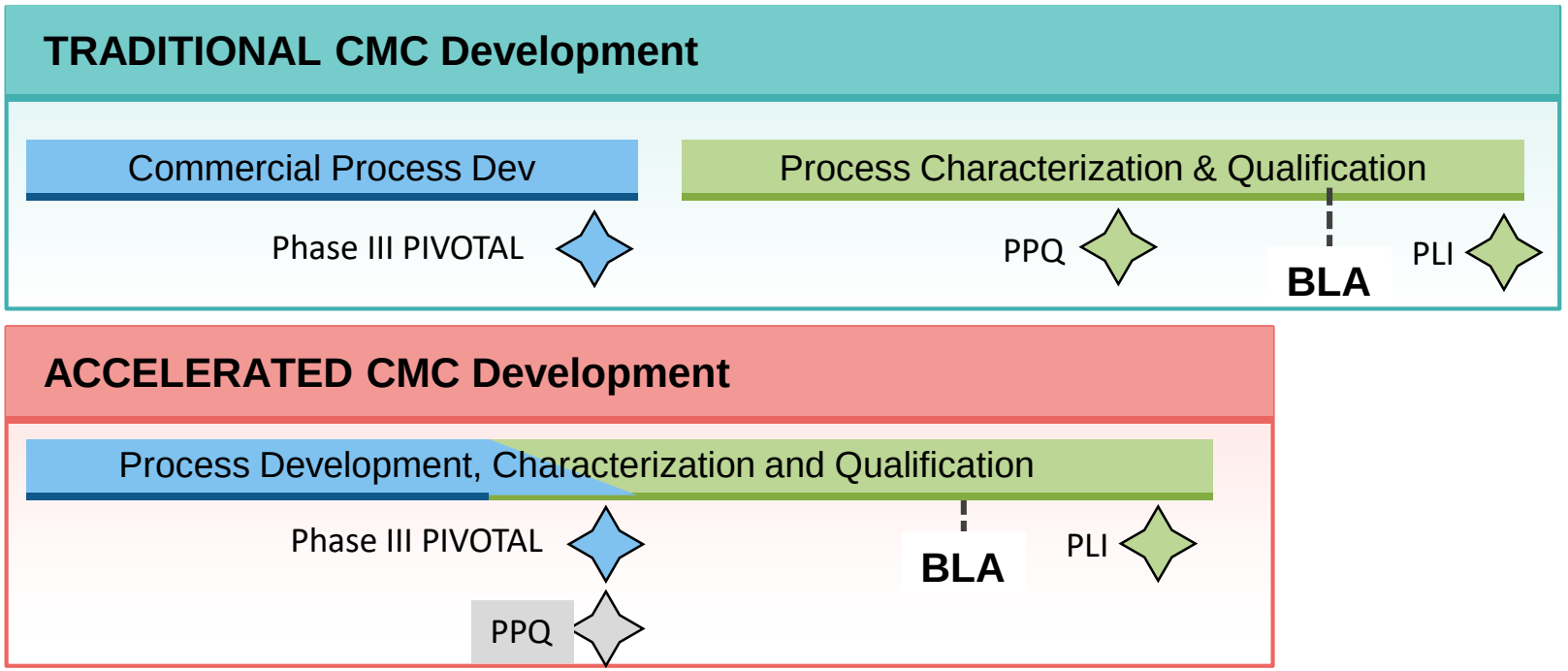
- PPQ performed to demonstrate the reproducibility of the commercial manufacturing process, acceptable process performance and product quality
- PPQ campaign is typically run late in development after pivotal supply (or resupply) campaign(s) conducted.



Opportunity Statement

- Data analysis from campaign has potential to fall on critical path for BLA
- Material from PPQ may not be needed for lower volume products
- Campaign often takes up precious time in commercial plants.
  - Historically consisted of anywhere between 4 – 9 runs.
- Significant run cost
  - Clinical manufacturing campaign = $
  - PPQ campaign = $$$ & additional FTE
- Can we rethink how we execute PPQ?

Enabler to CMC Acceleration



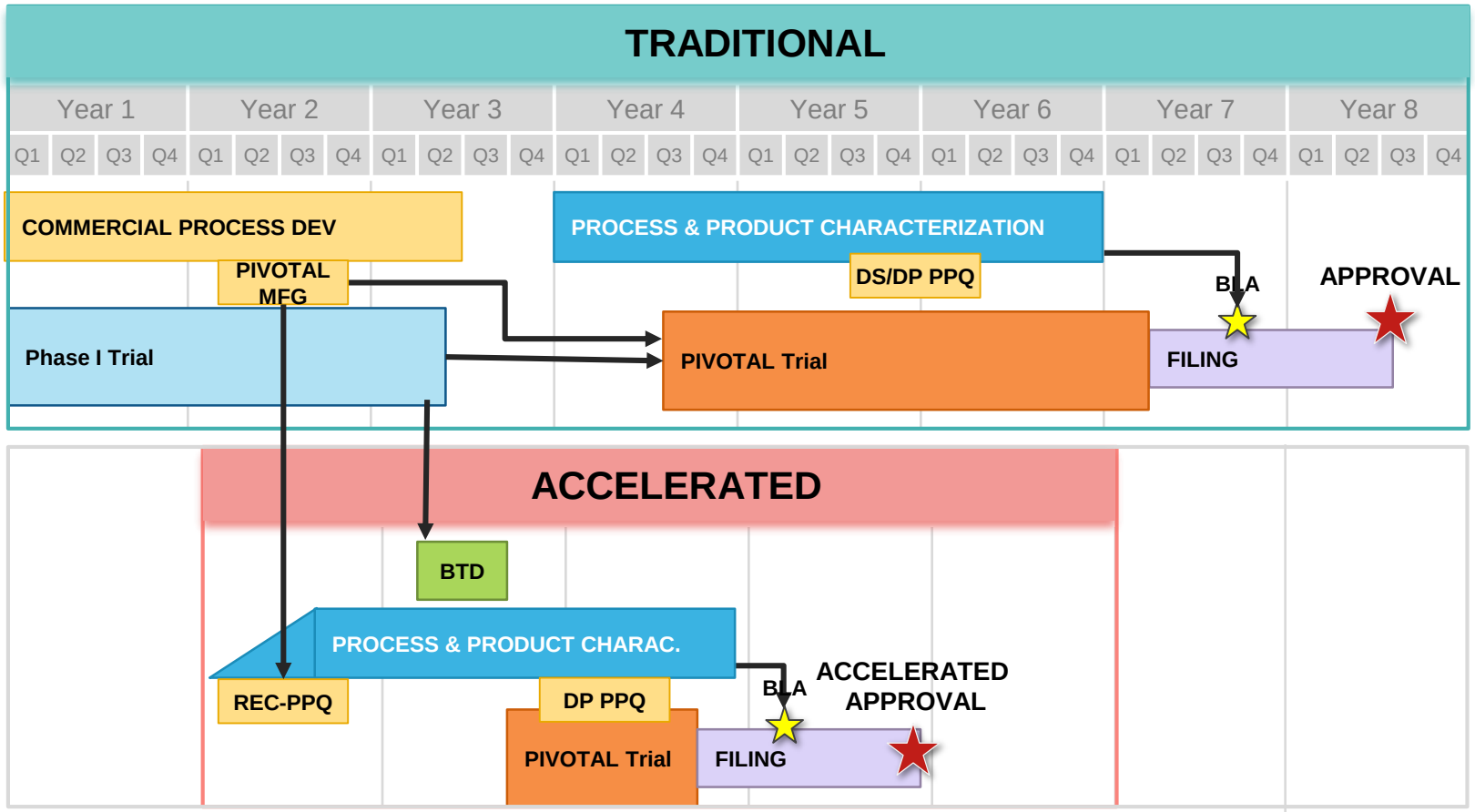
Additional flexibility, speed and savings realized when combining the Phase III and PPQ campaigns

Introduce the Registrational Enabling Campaign (REC)

- Consists of accelerating registration campaign (PPQ) earlier into development
- Leverage first pivotal DS campaign (n=3 to:

  - Fulfill partial and/or complete PPQ requirements
  - Supply clinical DP campaign and/or DP PPQ in anticipated launch facility
- Key Benefits
  - Enables acceleration
    - Early investment in large scale BLA enabling studies
  - Minimize full-scale DS runs needed for traditional PPQ (reduce cost & increased capacity)

An antibody in early development with potential for Registration Enabling Campaign



Ideal candidate for REC:

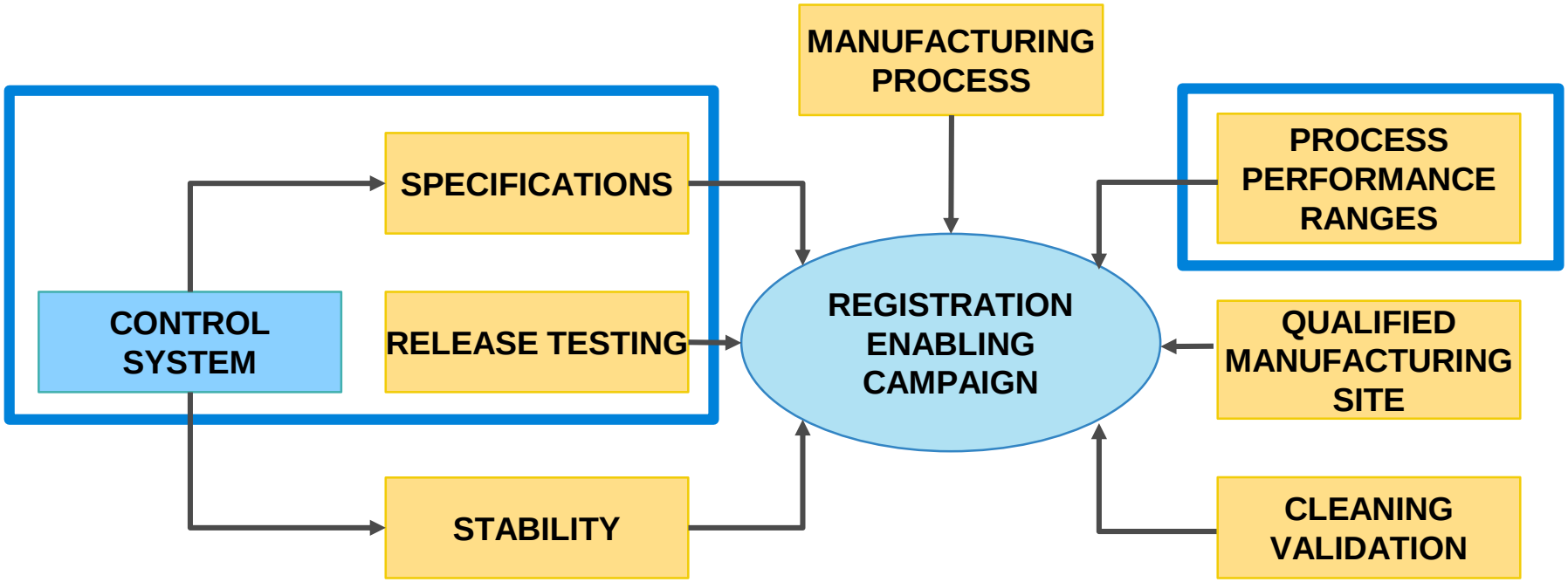
1. Clinical plan with potential need for CMC acceleration based on efficacy
2. **Low Volume:** Limited need for future supply campaigns
3. **No planned site changes** between Pivotal and Launch

Product Assumptions to Enable REC/PPQ

- Scaled up and locked commercial process with no changes post campaign
- Launch site is same as that used to make clinical material
- Low volume/demand at launch
- Phase III campaign executed as clinical campaign with PPQ prerequisite elements prospectively defined

- Leverage phase III control system
- Process characterization concurrent with and post campaign
- DS material to supply clinical DP for phase III and subsequent DP PPQ in anticipated launch facility

Considerations for Registration Enabling Campaign



Strategy for Control System and Process Performance were identified as two main challenges for a REC

Prospective Criteria for REC-PPQ

A REC requires early definition of Product Quality and Process Performance acceptance criteria

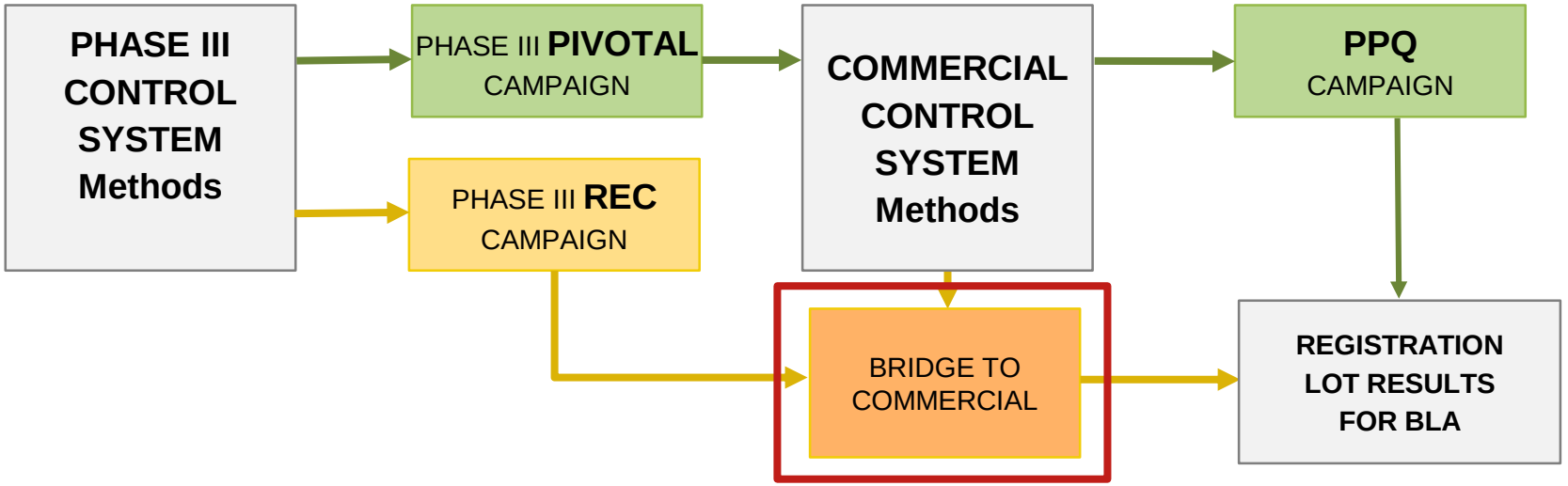
Process Performance Ranges from Limited Data

- Limited data set available for process parameters (KPIs & CPPs).
  - Platform Processes
  - Prior/Platform Knowledge
  - Phase III pilot scale data (n=3)

- Additional data to be subsequently generated from:
  - Unit Operation Process Characterization Studies (DOEs)
  - PPQ and PLI production campaigns

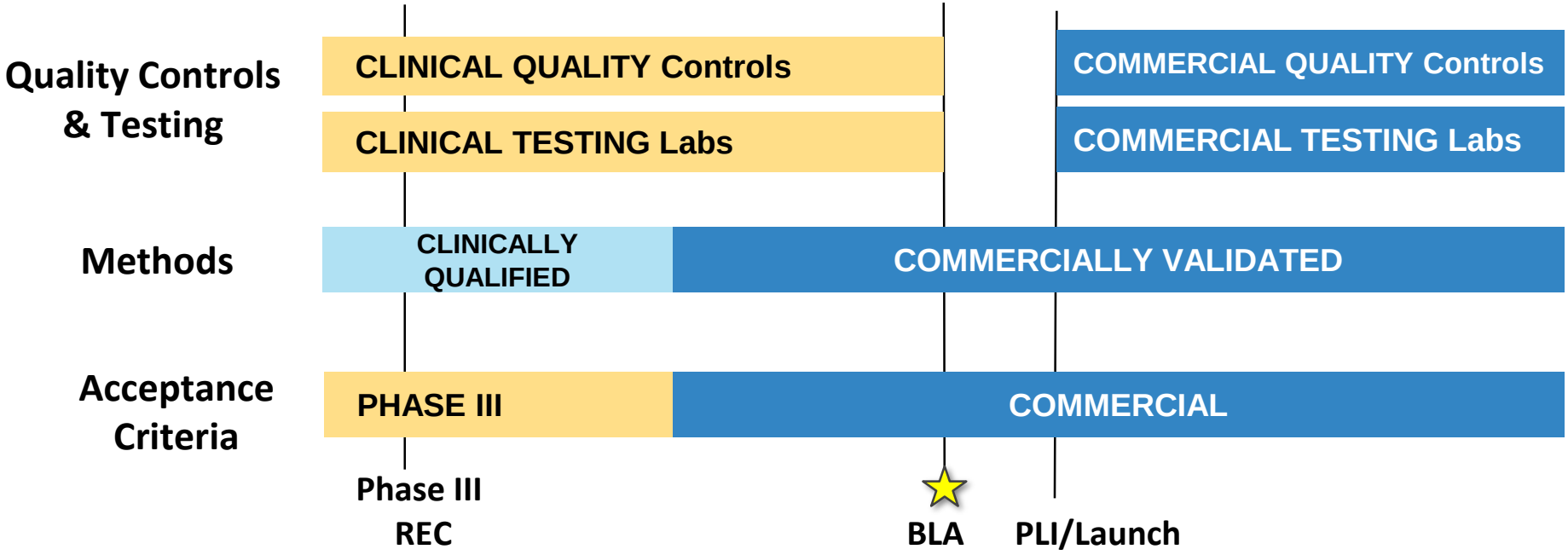
- Include retrospective analysis for PPQ batches
  - Newly defined CPPs/KPIs and/or updated ranges
  - Newly defined CQAs and/or updated acceptable ranges

REC-PPQ Control System Strategy



Commercial Control System Methods will be validated after the REC-PPQ and may leverage bridging studies where new/modified methods are used

Registration Enabling Campaign Specifications and Testing



Commercial specifications will be updated prior to submission and assessed against REC-PPQ clinical testing data

Conclusion

- Many drivers and potential pathways for accelerated CMC development
- Accelerated development strategies require early investment decisions
- Molecules need to be carefully selected for prioritization and strategies revisited often
- Early feedback from Health Authorities to align on Accelerated Development strategy is critical for success
- Defining PPQ ranges with limited data is a challenge, but can be mitigated with updates as data is available
- Using of Phase III Control System can reduce the early investment risk and allows for efficient bridging to Commercial systems prior to BLA and PLI

Expanding the pivotal manufacturing campaign to meet PPQ requirements can be a key enabler of CMC acceleration

Acknowledgements

REC PPQ Core Team Members

Team lead: Josh Grieco (PTDQ)
PVK – Monica Lent
ADQC – John Eschelbach
LSCC – Steve Meier
LSP – Susan Fisher / Sherrie Curtis
LSPD – Fred Lim
QPL – Patricia Lufburrow
SSF QC – Daniel Kelati
SSF Tech – Jody Logan
TPM – Mark Guzman
DS MSAT – Terry Hudson / Mike Chan
DP MSAT – Courtney Hill
SSF QEV – Jean Harms
LS Form – Vikas Sharma
PTR – Vandana Chauhan/Kathy Francissen
PACV – Tim Spirakes
QC Stability – Vida Echon
IMP QPL – Alice Yee
Reg Policy – Earl Dye
ORDP Support - Ivneet Bhullar

Product AD Planning Team

John Eschelbach (AD Planning Lead)
Trevor Swartz (Development lead)
Anu Bansal (Launch lead)
Josh Grieco
Susan Fischer
Steve Meier
Christine Wu
Polly Mak
Heater Zavatson
Bill Lai

Accelerated Development Sponsors

Brian Kelley
Dan Hagewiesche
Diane Hagerty
Jennifer Mercer

Doing now what patients need next