Acceleration to the Clinic and market in the post-COVID Era

Cell Culture Engineering XVIII
April 24, 2023

Nick Abu-Absi, AbbVie

Shahid Rameez, Merck

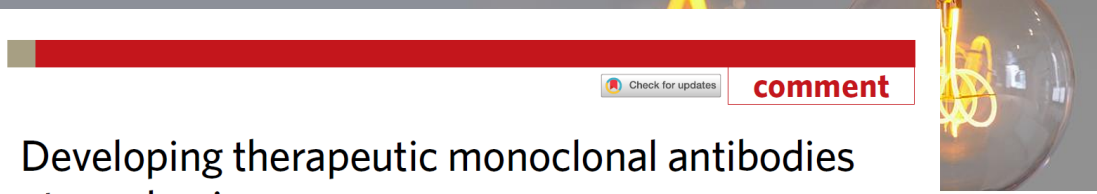
Weichang Zhou, WuXi

Special Thanks to Janani Narayan (University of Minnesota) and Jayanth Venkatarama Reddy (University of Delaware) for their contributions.

COVID sucked, but…

- Rapid Roll out of technology platforms to enable remote work
- On-line shopping and delivery
- Remote get togethers with friends and family
- Rapid development and roll-out of mAb treatments
- mRNA vaccines

How fast can we go?



*Nature Biotechnology – April 2020

- “There may be opportunities for substantially faster timelines arising from a combination of the latest technological advances with acceptance of higher business risk or costs without an increased risk profile to patients”
- “I propose that the answer could be 5-6 months rather than 10-12 months”
- Levers
  - Discovery platforms for rapid lead mAbs (IgG1s)
  - Cell Line Development
  - Platform Processes
  - Business Risks
    - Cell bank testing, fast entry to GMP and rapid scale up
  - Quality and Regulatory
    - Conditional release procedures, Prioritized testing, rolling IND submissions

How fast did we go?

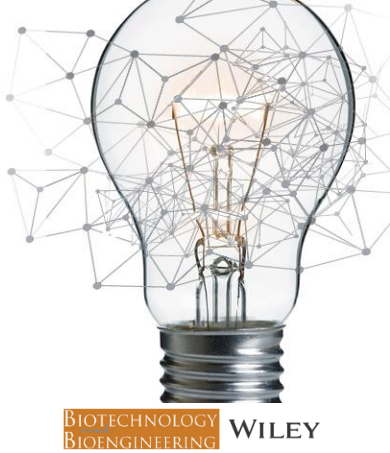
AccBio 2021

- Regeneron, Eli Lilly - < 2 months to IND
- Astra Zeneca – 3.5 months IND
- WuXi – 3-6 months to IND
    - Robust platforms
    - Non-clonal pools for tox and clinical supply
    - Business risks
    - Platform and Prior Knowledge to reduce PC studies
    - Concurrent timelines for development, tech transfer, process validation

Literature

- BMS
    - 6 months to IND
    - Path for 2-4 yrs to BLA
- MerckSerono – 4.5 months IND
    - Non-clonal pools

We Went Really Fast.



REVIEW

BIOTECHNOLOGY PROGRESS

The pandemic and resilience for the future: AccBio 2021

Āine T. McGovern[1] | Cleo M. Salisbury[1] | Gregg B. Nyberg[2]

ARTICLE

BIOTECHNOLOGY BIOENGINEERING WILEY

Accelerated cell culture process development and characterization for cilgavimab/tixagevimab (AZD7442) for the prevention and treatment of COVID-19

Michael W. Handlogten[1] | Stefanie Bosley[1] | Sarah Dunn[2] | Jie Zhu[1] | Allison Lee-O'Brien[1] | Lina Li[1] | Jamy Therres[1] | Lina Chakrabarti[1] | Bijay Khanal[1] | Rachel Mowery[1] | Subhashini Arumugam[1] | Judith Klover[1] | Jason Reier[1] | Diane Hatton[2] | Albert Schmelzer[1]

MABS
2022, VOL. 14, NO. 1, e2060724 (11 pages)
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Taylor & Francis Group

REPORT

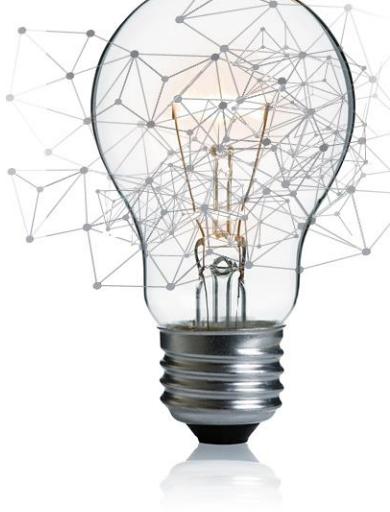
OPEN ACCESS Check for updates

Upstream cell culture process characterization and in-process control strategy development at pandemic speed

Jianlin Xu, Jianfa Ou, Kyle P. McHugh, Michael C. Borys, and Anurag Khetan

Biologics Development, Global Product Development and Supply, Bristol Myers Squibb, Devens, MA, USA

We Went Really Fast.



RESEARCH ARTICLE

BIOTECHNOLOGY PROGRESS

Reshaping cell line development and CMC strategy for fast responses to pandemic outbreak

Zheng Zhang | Ji Chen | Junghao Wang | Qiao Gao | Zhujun Ma | Shurong Xu | Li Zhang | Jill Cai | Weichang Zhou

ARTICLE

BIOTECHNOLOGY BIOENGINEERING WILEY

Rapidly accelerated development of neutralizing COVID-19 antibodies by reducing cell line and CMC development timelines

Kee Wee Tan | Pengfei Ji | Zichen Qian | Qiao Gao | Shuai Wang | Qin Li | Mingzhu Gu | Qi Zhang | Chengjian Hou | Yang Huang | Dujuan Lian | Junghao Wang | Zheng Zhang | Sam Zhang | Jiansheng Wu | Weichang Zhou

We Went Really Fast.

BIOTECHNOLOGY PROGRESS

REVIEW

Applied Cellular Physiology and Metabolic Engineering

Accelerated CMC workflows to enable speed to clinic in the COVID-19 era: A multi-company view from the biopharmaceutical industry

Matthew F. Higgins[1] | Nicholas Abu-Absi[2] | Elena Gontarz[3] | Ingo H. Gorr[4] | Klaus Kaiser[5] | Pramthesh Patel[6] | Frank Ritacco[3] | Patrick Sheehy[7] | Balakumar Thangaraj[8] | Tony Gill[1]

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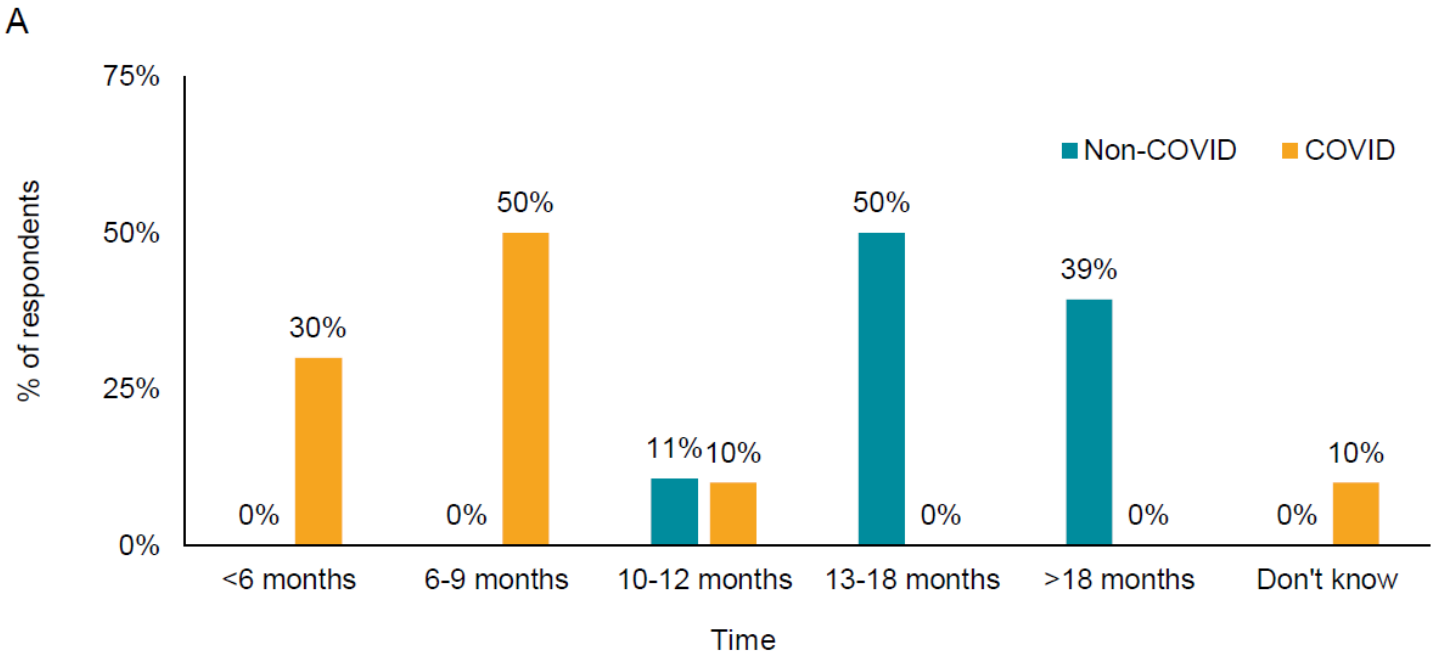
ScienceDirect

Current Opinion in Biotechnology

Monoclonal antibody therapies for COVID-19: lessons learned and implications for the development of future products☆

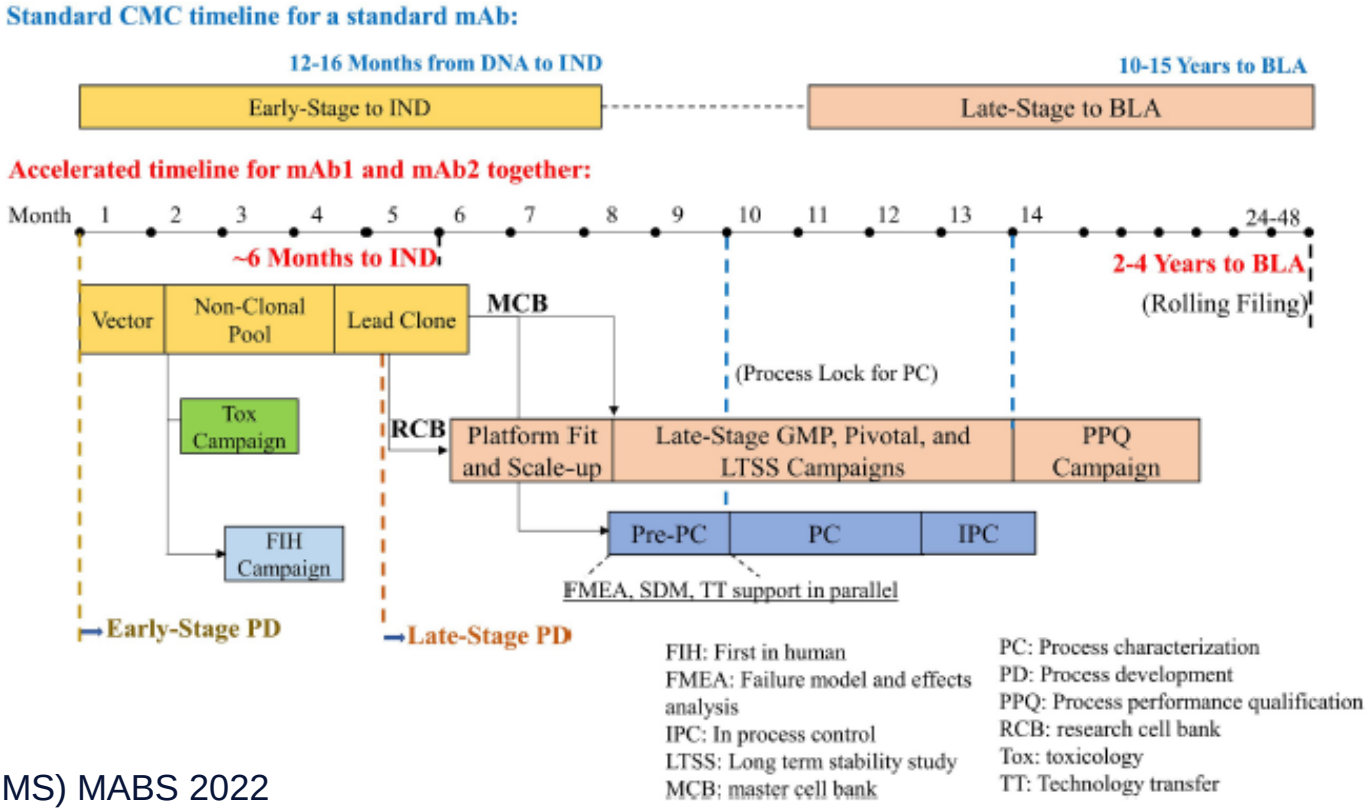
Brian Kelley[1], Pam De Moor[2], Kristen Douglas[1], Todd Renshaw[1] and Stacey Traviglia[1]

Timelines to IND for COVID Programs across Industry



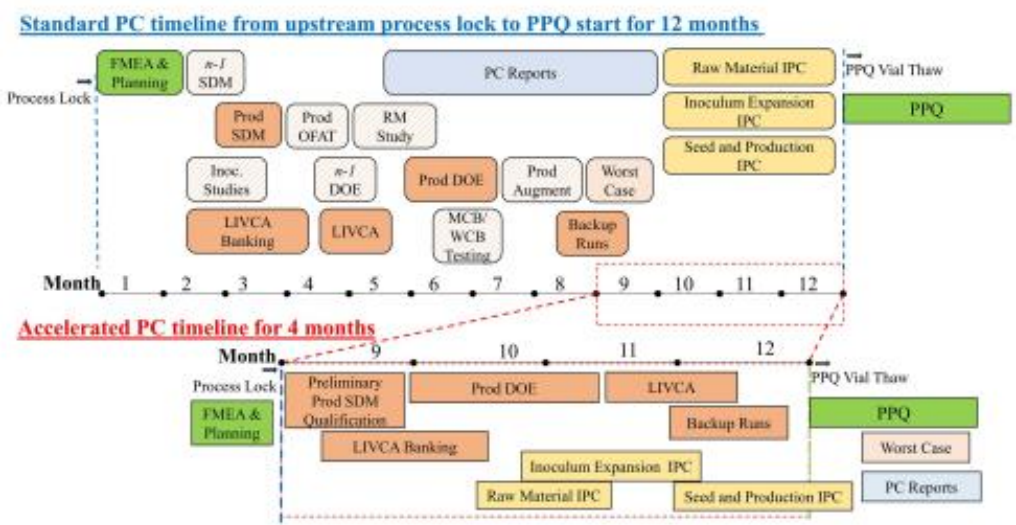
*From Speed to Clinic Benchmarking Survey from BioPhorum Development Group published in Biotechnology Progress

Summary of Early and Late Stage Levers



Xu et al. (BMS) MABS 2022

Late Stage Levers for COVID Acceleration



Xu et al. MABS 2022, VOL. 14, NO. 1, e2060724

Heavy Reliance on Platform

No process optimization was performed with robustness assumed.

Reduced/Tiered Process Characterization

Heavy reliance on platform and prior knowledge to significantly reduce process characterization experiments. Divide process characterization into two or more tiers – PPQ and BLA enabling

- **Will similar risk tolerance be maintained going forward?**

How to enable sustained speed to the clinic without significant risk?

- **The resources of the world were behind rapid development and authorization of vaccines and treatments**
  - **Company resources were aligned**
  - **Raw materials were allocated to COVID programs by vendors**
  - **Partnerships across companies**
  - **Testing slots were prioritized to COVID programs by CROs**
  - **Manufacturing capacity at CMOs prioritized**
  - **Heavy reliance on platforms and prior knowledge**
  - **Health Authorities aligned with industry on increasing speed, but without significant risk to patients**

➢ **Conscious acceptance of business risk and intense resource effort**

➢ **How do we apply lessons from the COVID pandemic in a way that is sustainable across a pipeline?**

Breakout Session #1

Speed Levers
20 Minutes

Cell Line Development Platforms/Technologies

What does the optimal Cell Line Development Workflow Look Like to maintain speed to FIH without significant risk mitigation or additional resources?

- List key elements that make up the optimal platform and workflow
- List the infrastructure and know how needed to enable key elements
    - How widely available?
- List significant risk mitigation activities that may be needed later

Potential topics for discussion

- Platforms
    - E.g. - Transposases, Targeted Integration
- Technologies
    - E.g. - Automation, Berkeley Lights Beacon, AMBR
- Workflow examples
    - Number of candidate molecules to start CLD
    - Use of non-clonal, transient lines for tox?
    - Use of non-clonal, transient lines for clinic?
    - Cell Bank Release Testing – Technologies, use of CROs…

Process Development Strategies

Process Development Strategies

- Single Cycle Development
    - What does this look like in practice? Types of changes and how/when to enable?
    - What are infrastructure, platform knowledge requirements
    - Are there scenarios where this may not be appropriate
- Traditional early followed by late stage development
    - Is this sustainable?
    - What is needed to move towards Single Cycle Development or more sustainable workflows?
    - Are there scenarios where this is necessary?

PD Workflow Elements

- Intensification/PAT
    - Do intensification/PAT have role to play in PD efficiency?
- Process/Hybrid Modeling
    - Applications
    - Expertise and data requirements to enable
- PD Toolboxes
    - Types – e.g. CQA tuning, productivity improvements, process optimization
    - When to apply – e.g. for specific molecular formats or therapeutic areas

Process Characterization/Validation Strategies

Process Characterization

- Platform and Prior Knowledge
  - Define platform vs. prior knowledge
- List applications of prior knowledge – e.g. reduce process characterization studies
  - Define required datasets – e.g. # of molecules, structured vs unstructured datasets, etc…
  - Discuss how this would be presented to support control strategy in filing

Process Performance Qualification

- PPQ in parallel with manufacture of pivotal clinical trial material
  - Discuss requirements to enable PPQ vs BLA – i.e. tiered process characterization approach)
  - Discuss risks and potential mitigating actions

Continued Process Verification

- Will acceleration to PPQ filing result in more substantial CPV commitments?
- Are there toolboxes to ease CPV burden?
  - In-line/on-line/at-line controls
  - PAT
  - Multivariate statistical process controls
- What is infrastructure required?

Breakout Session Report Out

- High level summary of levers discussed
  - Rank in order of importance
- Infrastructure required
  - Capabilities/equipment
  - Resources
  - Datasets
- Pros and Cons
  - Are there scenarios where certain strategies or workflow elements don’t make sense
  - What are risks and potential mitigations of applying a particular speed lever
- 2-3 minutes per breakout table (15 minutes total)
- Designate scribe for note-taking

Breakout Session #2

Case Studies
20 minutes

Sustainable FIH Platform Timelines

- **Pre-pandemic FIH timelines were ~12 months from DNA to IND**
- **COVID FIH timelines were ~5 months from DNA to IND**

➢ **Can and should we push FIH timelines faster going forward**

  ➢ **What is the right blend of speed, quality, cost? What business risks are acceptable?**

- Map out new time to FIH that is sustainable across a pipeline
  - DNA to tox material supply
    - How many molecules to start CLD with, where in the workflow to finalize lead?
    - What are technologies, platform elements needed?
  - Tox to GMP
    - Transient, non-clonal, clonal line?
    - MCB release
    - Facility requirements
  - GMP to IND
    - DS/DP release
    - Stability Data
    - IND templates

Sustainable non-Platform FIH Timelines

- **Novel molecular formats are becoming increasing percentage of biologics portfolios**

  - ➢ **How fast can we sustainably get from DNA to IND for non-mAbs?**

- Are there particular formats that can be platformed to achieve similar timelines as mAbs?
  - E.g. – ADCs, bi-specifics, Fc-fusions?
  - How can this be enabled?
  - Any sacrifice to speed, quality or cost requiring additional mitigation vs. mAbs?
  - Is there increased development/validation cost required after FIH?

- Are there modalities that require longer timelines? How much longer is needed?
  - What additional workflow elements are required
    - E.g. - PD toolboxes
    - Any additional risk mitigation activities required?
    - Is there increased development/validation cost required after FIH?

Sustainable Platform Fast to Market Workflows

- **Process development and characterization studies were significantly reduced for COVID programs**
- **PPQ performed using clinical batches rather than separate campaigns (traditional approach) for COVID programs**

➢ **What are optimal late stage development workflows going forward?**

  ➢ **What is the right blend of speed, quality, cost? What business risks are acceptable in terms of CPV/post-marketing activities?**

- Map out new workflows for late stage development and commercialization for platform programs
  - Is process optimization performed?
  - PPQ enabling activities
    - Platform/prior knowledge applications
  - Separate clinical and PPQ campaigns or pursue in parallel?
  - BLA enabling activities
  - CPV/Post-marketing activities

Sustainable Non-Platform Fast to Market Workflows

- **Novel molecular formats are becoming increasing percentage of biologics portfolios**

➢ **What are optimal late stage development workflows going forward?**

➢ **What is the right blend of speed, quality, cost? What business risks are acceptable in terms of CPV/post-marketing activities?**

- Map out new workflows for late stage development and commercialization for non-platform programs
  - How to determine scope of commercial process development activities? Are there classes of molecular formats (e.g. ADCs, bi-specifics, etc…) more or less amenable to single cycle development?
  - PPQ enabling activities
    - Challenges associated with leveraging Prior Knowledge to reduce process characterization burden
  - Separate clinical and PPQ campaigns or pursue in parallel?
  - BLA enabling activities
  - CPV/Post-marketing activities

Breakout Session #2 Report Out

- What are sustainable timelines going forward?

- What combination of speed levers can be applied?
  - Are there any speed levers that should not be applied? Why?
  - Are there any speed levers that require significant resources/infrastructure/expertise?

- What is acceptable level of business risk going forward?
  - Higher than pre-COVID or about the same?
  - What are these risks and mitigating actions?

- 2-3 minutes per breakout table (15 minutes total)
- Designate scribe for note-taking

Key Outcomes

- Early-stage strategies
  - Transfection
    - Lever to pull: stable integration
    - Move forward with transient transfection in pools while performing quality control on plasmids (codon optimization, etc.)
  - Automation
    - Lever to pull: fed-batch for screening
    - Utilize Beacon/AMBR for single cell cloning
  - Genome integration
    - Lever to pull: targeted integration
    - Transposase (semi-targeted integration) enables pool diversity, and faster titers
    - If employ targeted integration, have multiple cell lines ready for each candidate

- Late-stage strategies
  - Timelines
    - Lever: sequential progression
    - i.e. Move cell line 1 into clinic, while progress with cell line 2
  - Toxicology
    - Lever to pull: clones
    - Pools sufficient for testing where titer may not be important
  - Platform
    - Lever to pull: biphasic
    - Single cycle development, especially when CQAs are known; leverage platform and prior knowledge (FMEA)
    - Perform late-stage biphasic only when early-stage doesn't meet requirements
    - *In silico* can be leveraged to deepen molecule understanding
  - Process characterization
    - Lever to pull: understanding of validation ranges
    - Important to develop PPQ, even with limited knowledge of appropriate quality ranges, then expand further after characterization

Key Outcomes

- Sustainable non-platform fast process, acceptable risks?
- Optimal workflow dependent on how different product is from previous products
- Remove redundant studies and optimize use of resources (samples)
- If robust PAT can be performed upfront, time to market can be minimized

- Fast to market (platform?)
- 9-12 months to FIH may be reasonable
- Develop process model using prior knowledge
- Limited process validation necessary, understand product stability from clinical studies
- Digital database helps
- Initiate characterization along with tech transfer to supply site
- Transfer to commercial site may take (2-3 years)
- Risk exists if characterization doesn’t fit the model and may create delays

- FIH (platform?)
- Leverage internal assets vs partners (can negotiate)
- Master cell bank tested before use in GMP vs before release vs before manufacturing

- FIH (non-platform)
- For non mABs
- Toxicity studies are limiting, so design better studies
- Define what is time 0 (what is DNA)
- Understand analytics and CQAs
- Leverage automation