Tracy Kinjerski and Steven Chamow, Ph.D.

CDMO Selection for Bispecific Antibody Development: A Case Study Matching Capabilities to Need

Chamow & Associates, Inc. San Mateo, CA USA

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Biopharmaceutical Product Development

Overview

- The Challenge
  - Client company/project
  - Target product profile
  - How to use a consultant in this process
- The Match
  - Considerations for candidate CDMOs
- Scope of Work
  - Development
  - GMP production
  - Timing of pre-IND meeting, IND
- Summary

Pre-reads

1. Judy Meyers, How to Find the Right CDMO Partner in Pharma, *Pharma Manufacturing,* Oct, 2019
2. Stephen Closs, Quality by Design: Working With Your Contract Manufacturer, *Chemistry Today* **32**, 10-13 (2014)
3. David Wilkerson, Outsourcing in Pharma and Biotech: Shifting to Contract Manufacturing and Development, *Zymewire* blog, 4 Mar 2020

The Challenge

The Client

- Small, venture-funded Bay Area biotechnology company
- Internal capabilities
  - POC research laboratory
  - No CMC development infrastructure
- Monoclonal antibody discovery platform
- Oncology focus

The Project

- Client company sought to develop pre-clinical mAb
  - Product
    - Humanized IgG1, not a bispecific
  - Hired external consulting group to execute CMC
    - Identify, evaluate, select and manage CDMO
    - Develop pre-IND strategy
    - Write CMC module of IND
  - Starting point
    - In silico amino acid sequence
    - Target product profile

Target Product Profile (TPP)

- “Needs checklist”
- Defines product characteristics
  - Product description
  - Indications and usage
  - Dosage and administration
  - Dosage forms and strengths
  - How supplied and handling
- Provided client with a roadmap to guide product development
  - Anticipated dose and clinical indications → amount needed for clinical studies → scale of production
  - Route of administration → type of formulation

Preclinical TPP

- Clinical indication – oncology
  Scale of production – 1000 or 2000 L
- Route of administration – infusion
  10 mg/mL liquid solution
  2-8 deg C storage

Characteristic	Detail
Product Information	
Product name	
Molecular description	Humanized IgG1/k
Biological activity	
Proposed mechanism of action	
Structural requirements	
DS Stability	24 mo -20 deg C
Dosage Form	Buffered liquid solution
DP Stability	36 mo 2-8 deg C
Route of Administration	Intravenous
Dosage Strength	10 mg/kg
Pharmacokinetics	
Container and Closure System	Glass vial
Production DS	
CDMO	
Cell line	CHO
Target productivity at harvest	3 g/L
Production scale (L)	2000L
Estimated overall yield (%)	80%
Batch size (kg)	4.8 kg
Production DP	
CDMO	
Estimated yield (%)	
Batch size (# vials)	
Forecast (projected demand for Ph3 clinical trials, launch and first 5 years on market)	
Labeling and Clinical Packaging	
Vendor	

The Match

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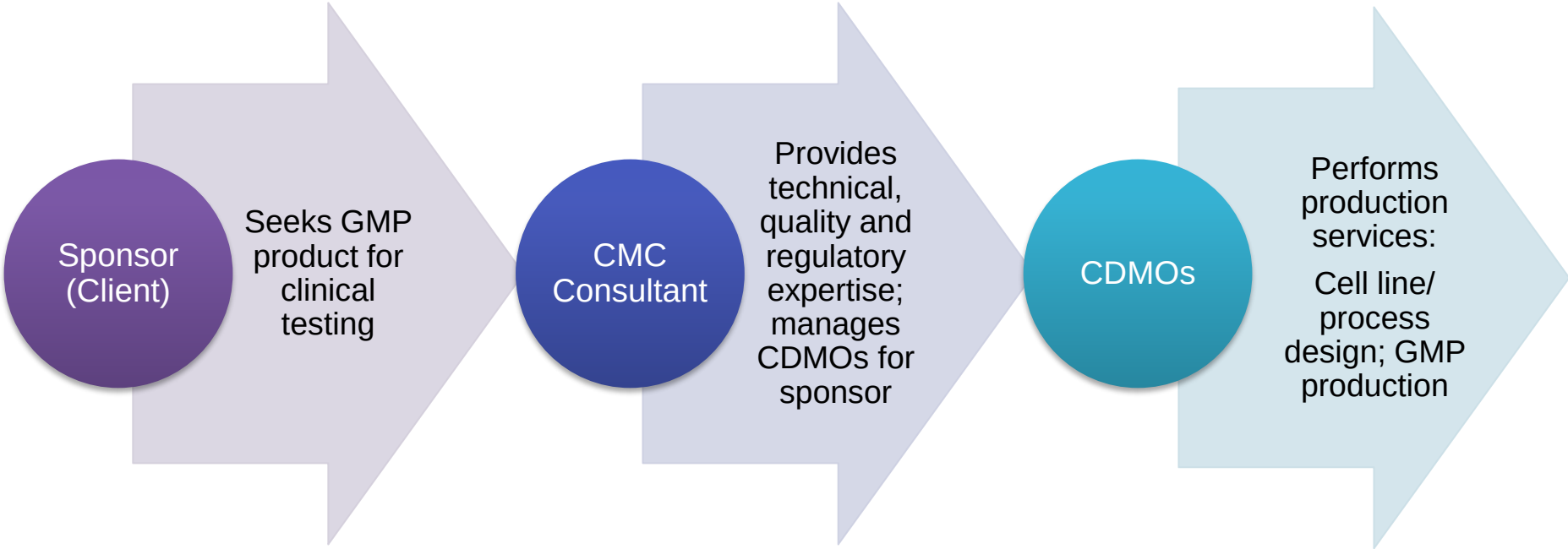
Use of CMC Consultants to Select and Manage CDMOs



We Evaluated CDMOs with Different Capabilities and Expertise

- Expertise varies
  - Monoclonal antibodies
  - Bispecifics
  - Enzymes
  - Cytokines
  - Growth factors
  - Fusion proteins (Fc, albumin)
  - ADCs
- Capabilities vary (e.g., one-stop shop or not)

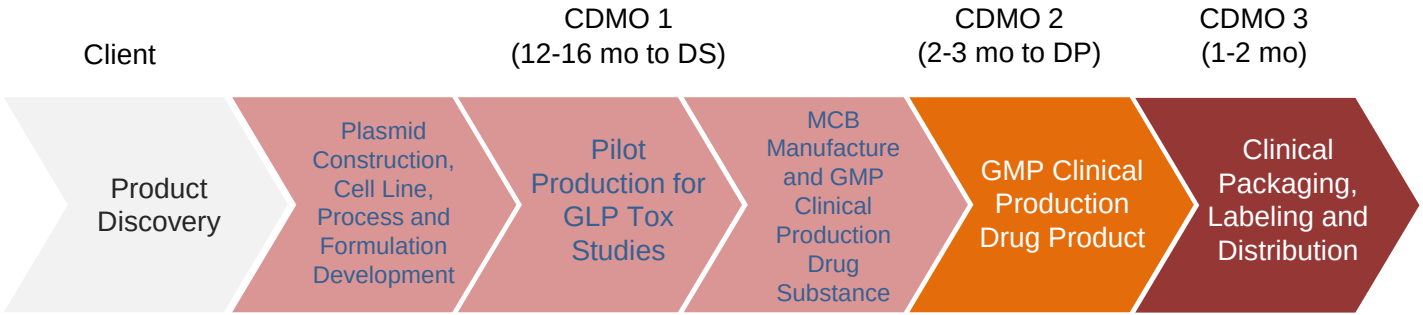
Factors in Matching Client to CDMO

- Phase of development
  - Phase 1/IND vs. Phase 3/commercial
- Priorities
  - Quality
  - Cost
  - Time
    - Considered that cost and time are trade-offs
- Cell line
  - Productivity
  - Terms of access
    - Proprietary vs. non-proprietary
    - Wanted a CDMO with proprietary technology
- Cell line development experience and success
    - Not all CDMOs are equally good at making cell lines (stability, productivity, etc..)

Factors (cont'd.)

- One-stop shop or different CDMOs
- Process development
- Formulation development
  - This formulation was straightforward
- Analytical methods/Stability
- MCB—production/characterization
- cGMP
  - DS
  - DP
- Other considerations
  - Capacity for manufacture
  - Scale up and scale of manufacture

Project Stages and Timeline



Overall duration from delivery of amino acid sequence to clinical trial material: 15-21 month

Scope of Work

The Starting Point…

Synthesizing cDNA from an amino acid sequence

mAb γ1 Heavy Chain

Amino Acid Sequence

MAVLGLLFCLVTFPSCVLSQVQLKESGPGLVAPSQSLSITCTVSGFSLTDYGVRWIRQPPGKGLEWLGVIWGGGSTYYNSALKSRLSISKDNSKSQVFLKMNSLQTDDTAMYYCAKEKRR
GYYYAMDYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKAEP
KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKTS

cDNA Sequence

ATG GCT GTC TTA GGG CTA CTC TTC TGC CTG GTG ACG TTC CCA AGC TGT GTC CTG TCC CAG GTG CAG CTG AAG GAG TCA GGA CCT GGC CTG GTG GCG CCC
TCA CAG AGC CTG TCC ATC ACA TGC ACT GTC TCA GGG TTC TCA TTA ACC GAC TAT GGT GTA AGG TGG ATT CGC CAG CCT CCA GGA AAG GGT CTG GAG TGG CTG
GGA GTA ATA TGG GGT GGT GGA AGC ACA TAC TAT AAT TCA GCT CTC AAA TCC AGA CTG AGC ATC AGC AAG GAC AAC TCC AAG AGC CAA GTT TTC TTA AAA ATG
AAC AGT CTG CAA ACT GAT GAC ACA GCC ATG TAC TAC TGT GCC AAA GAG AAA CGG AGG GGG TAT TAC TAT GCT ATG GAC TAC TGG GGT CAA GGA ACC TCA GTC
ACC GTC TCC TCA GCT AGC ACC AAG GGC CCA TCG GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG GGC TGC CTG GTC
AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC
TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC
AAG AAA GCA GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA
CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG GTC ACA TGC GTG GTG GTG GAC GTG AGC CAC GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG
GAC GGC GTG GAG GTG CAT AAT GCC AAG ACA AAG CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGG GTG GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC
TGG CTG AAT GGC AAG GAG TAC AAG TGC AAG GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA GAA
CCA CAG GTG TAC ACC CTG CCC CCA TCC CGG GAT GAG CTG ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC ATC GCC
GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC
GTG GAC AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT
CCG GGT AAA ACT AGT TGA

…To the Goal

Producing bulk drug substance and filled and labelled drug product

Scope of Work

Development

- Cell Line
  - cDNA synthesis and plasmid construction
  - Cell line
    - RCB
    - MCB
- Process
  - Upstream
  - Downstream
  - Formulation
- Analytical
  - Compendial
  - Product-specific
    - Platform methods
    - Potency

Scope of Work (cont'd.)

Scale Up and Clinical Production

- Tox production
  - Reference material
  - Preliminary DP stability
- Characterization of reference material
- GMP production of DS
  - Viral clearance study
  - ICH Stability
- GMP production of DP
  - ICH Stability
- Clinical labeling, packaging and distribution

Cell line and Process Development

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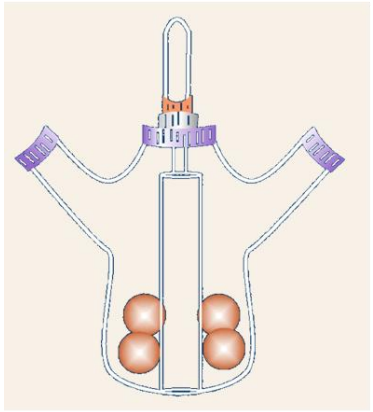
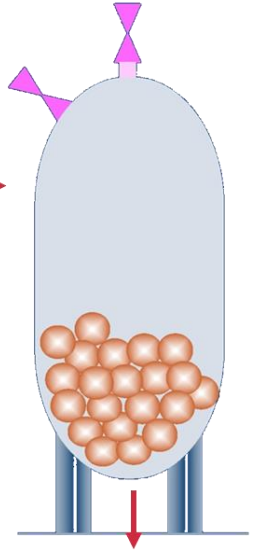
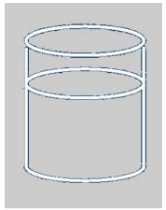
Elements of the Process



Cell line



Upstream process



Downstream process

Formulation and testing

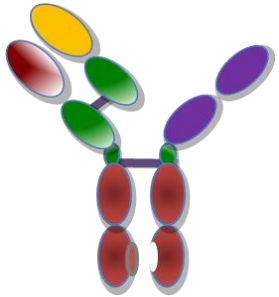
First Consideration: Cell Line/Expression System

Type of cell line	Expected productivity	Timeline*	Cell line stability	Cost components		
				Fee for service	Milestone payments	Royalty
Proprietary (requires license)	3-7 g/L, may require proprietary media	3-6 mo aa sequence to RCB	60-generation confirmation may not be critical path task	Yes	Yes	Few
Non-proprietary (public domain)	1-3 g/L, generally with commercial media	6-9 mo, aa sequence to RCB	60-generation confirmation of stability is critical path task	Yes	No	No

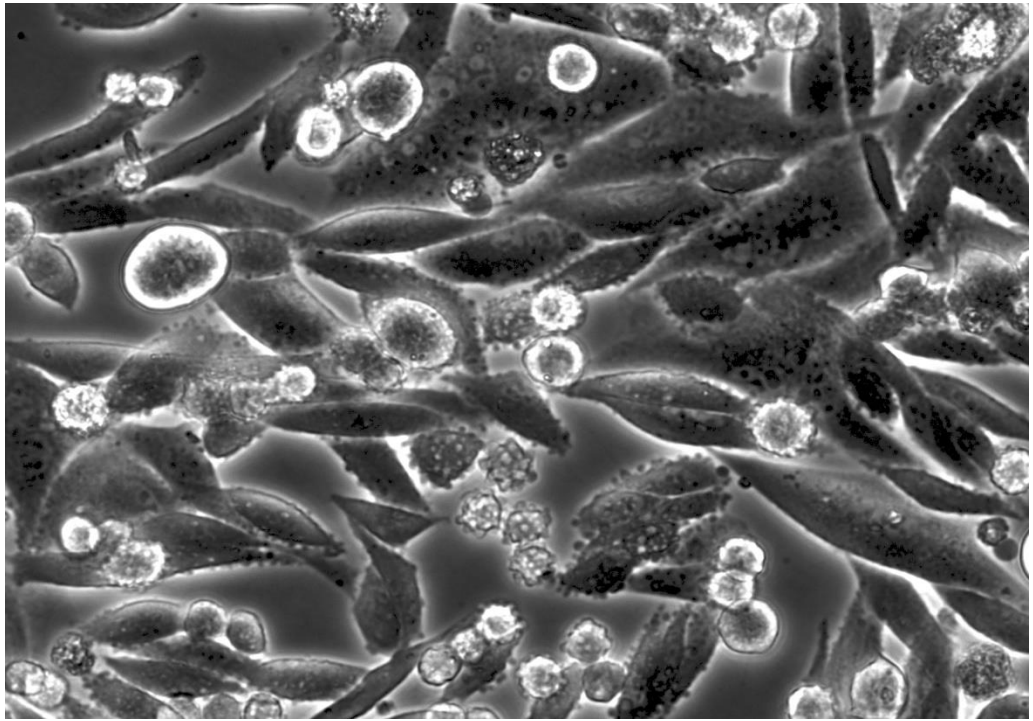
*Includes 1 mo for DNA codon optimization, synthesis + 1 mo for plasmid construction

Special Considerations for Bispecifics

- Vector design
  - Single vs. multiple plasmid system
    - Assembly of the oligomer may vary with differential expression of monomer chains
    - Chain ratio may need to be optimized
    - Multiple plasmids provide greatest flexibility
- Structure and stability
  - Implications for use of a platform process
  - Stability at extremes of pH
    - Acid stability required for capture on Protein A, low pH hold for virus inactivation
  - Purification complexities
    - Product variants as impurities
    - Removal of variants will define final polishing chromatography



We went with Chinese Hamster Ovary Cells/Proprietary Expression System



Maximizing Productivity of Cell Culture Process

- Titer (mg/L) is determined by accumulated cell mass x cell specific productivity

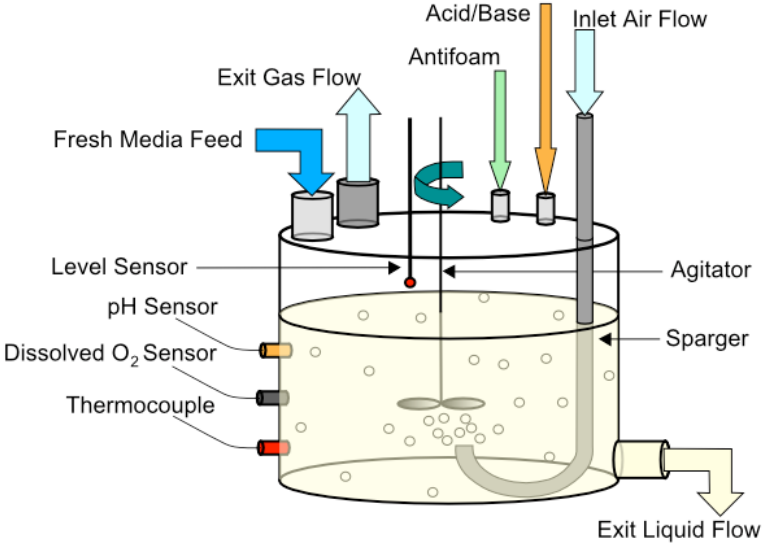
$$\text{Titer} = qp \bullet \int x dt$$

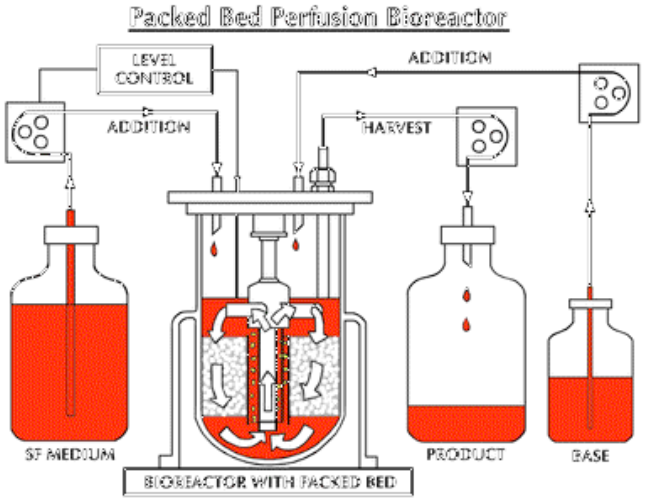
Where
qp = cell specific productivity
$\int x dt$ = cell mass

- A good process…
  - Starts with a highly productive cell line
  - And a cell culture process that produces high accumulated cell mass
    - Time in production phase with high cell viability
    - Timing and composition of feeds
      - Provide just-in-time nutrients and minimize waste products
    - Rate of agitation, oxygenation (sparging)

Cell Culture Process Design

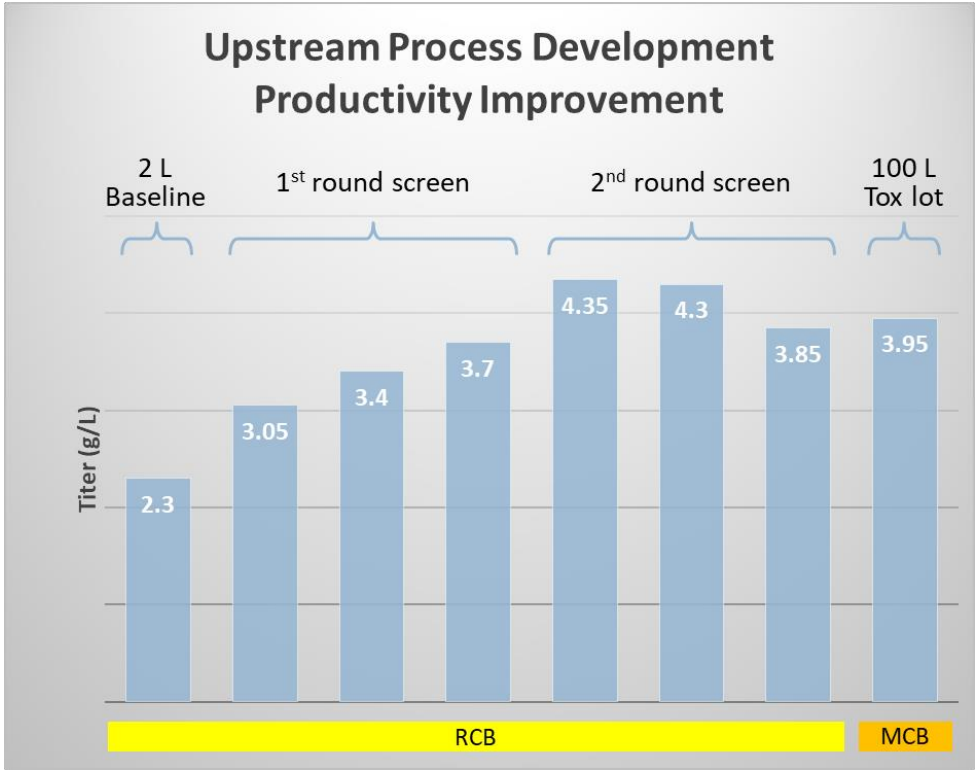
- **Fed-batch**
- Perfusion





Process Development Runs—Product Titer

- 2L confirmation batches (3)
- 100L pilot batch (tox)

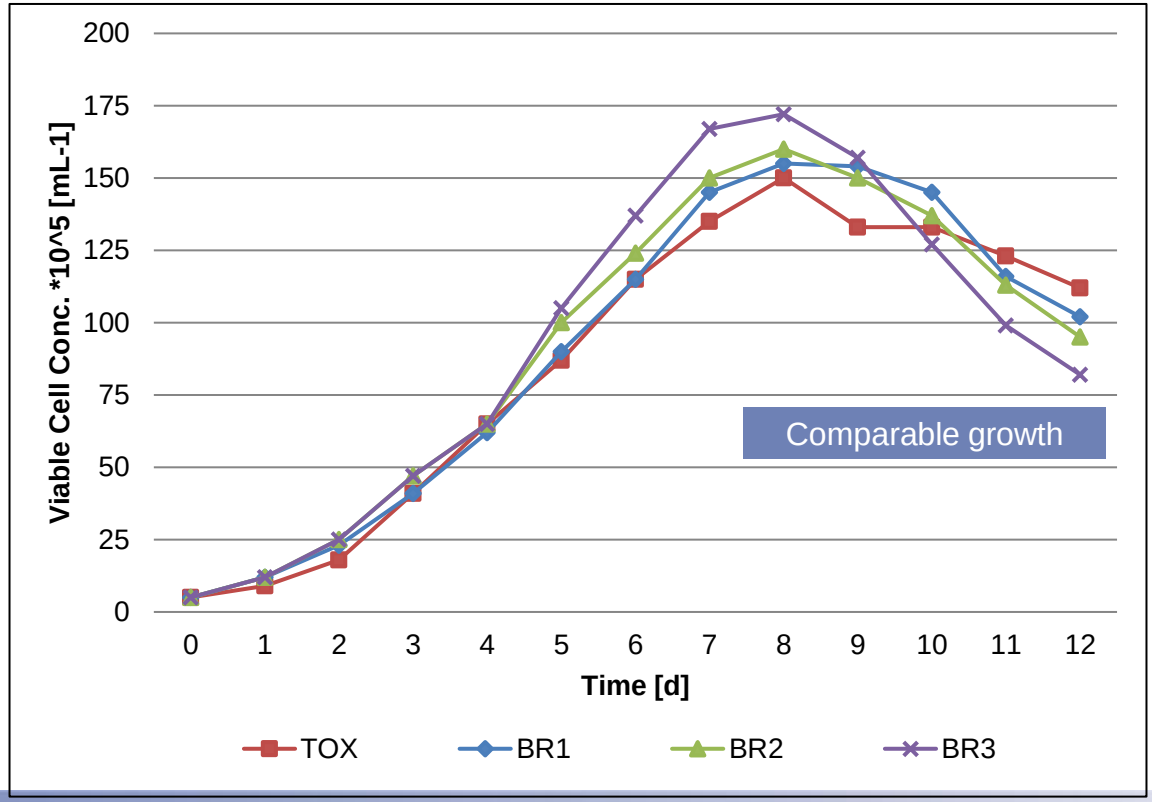


GMP Production

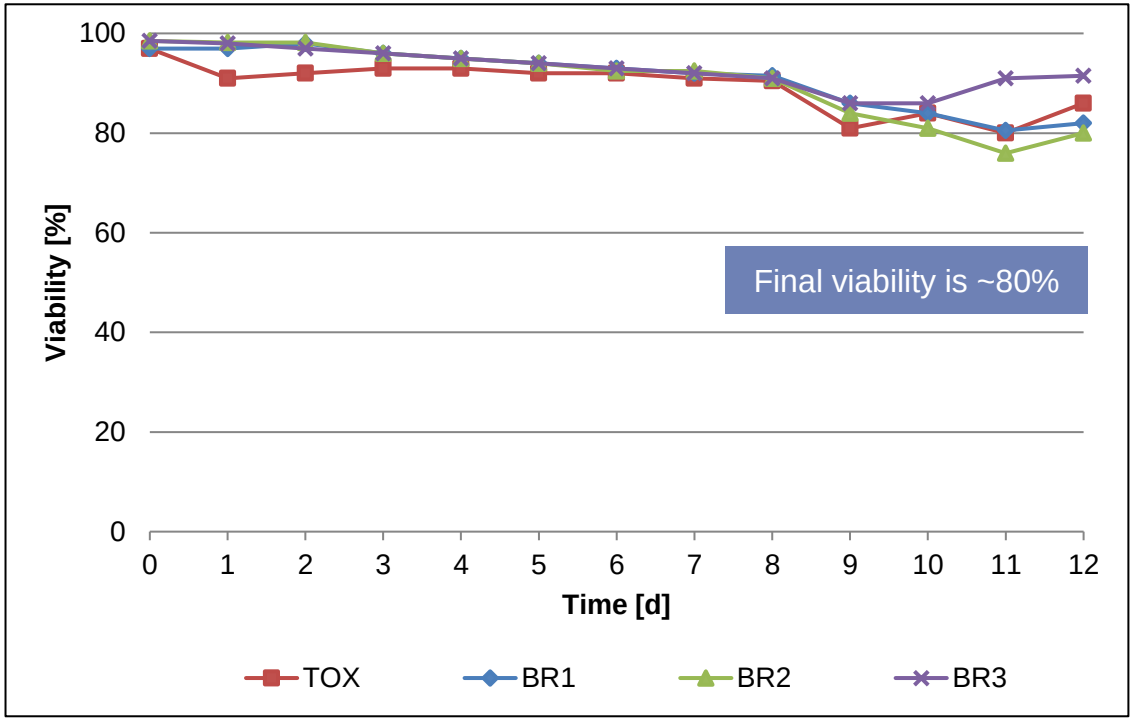
Summarizing the Scale Up

- Confirmation runs at 2 L bench scale
  - Performed with RCB
  - Confirmed performance of complete process
- Tox production at 100 L pilot scale
  - Performed with MCB
  - Pilot scale process reflects GMP process
    - Generates reference material
    - Preliminary DS, DP stability to support GMP stability
- GMP production at 2000 L
  - Performed with MCB
  - Samples taken for
    - Virus clearance study
    - DS, DP stability
  - Assay methods qualified

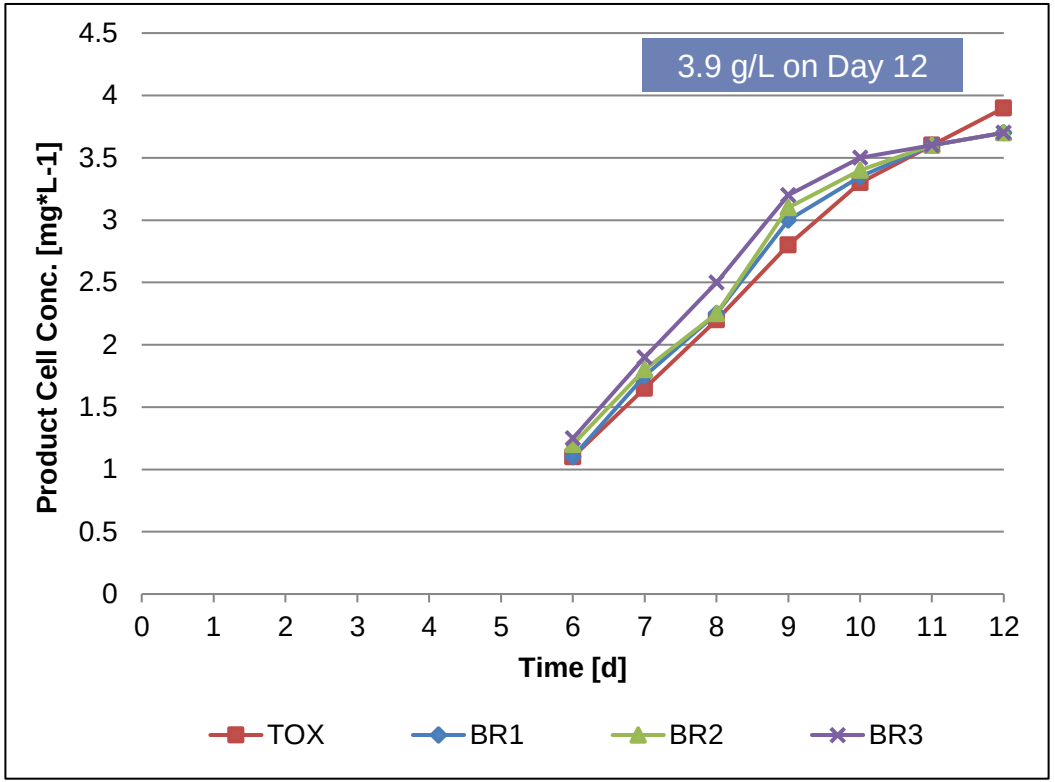
Confirmation Runs vs. Tox Batch – VCD



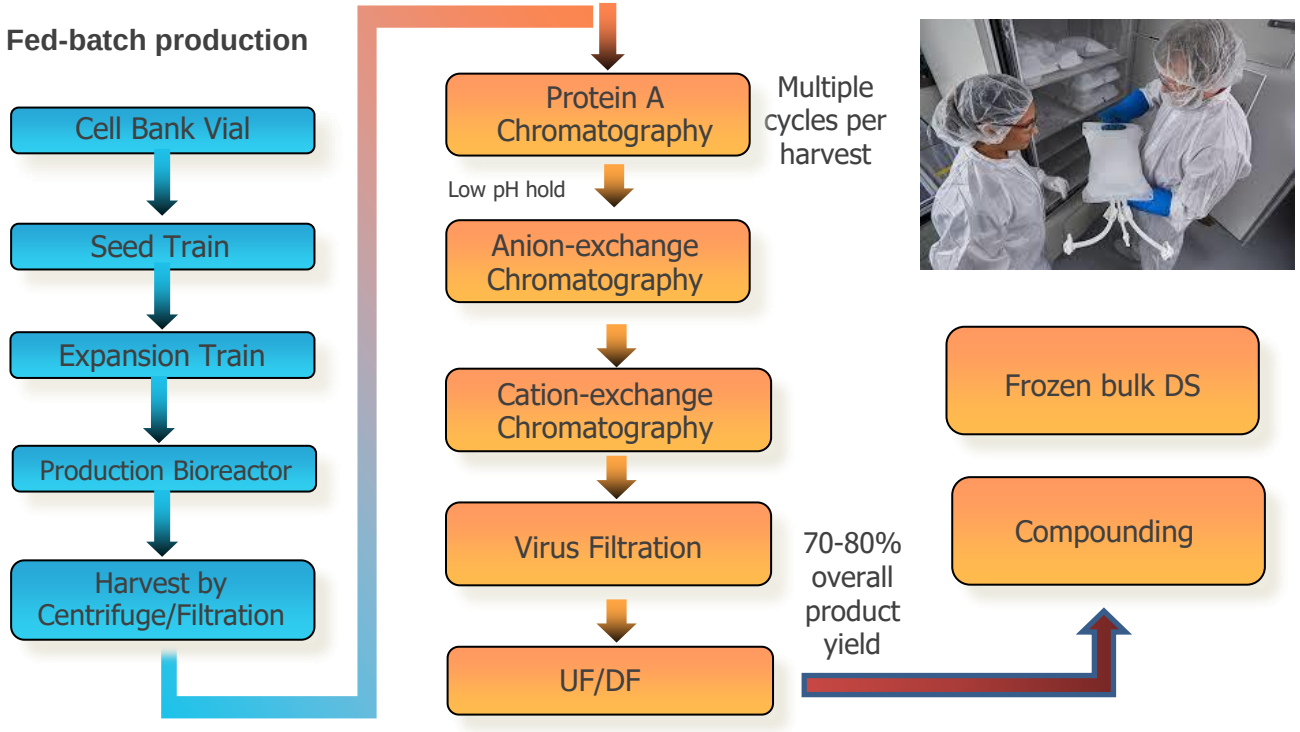
Confirmation Runs vs. Tox Batch – Viability



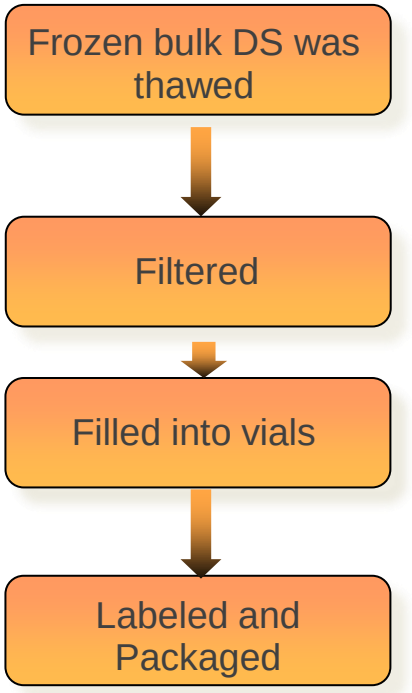
Confirmation Runs vs. Tox Batch – Titer



Summary of Process - mAb Bulk Drug Substance (DS)



Summary of Process - mAb Drug Product (DP)

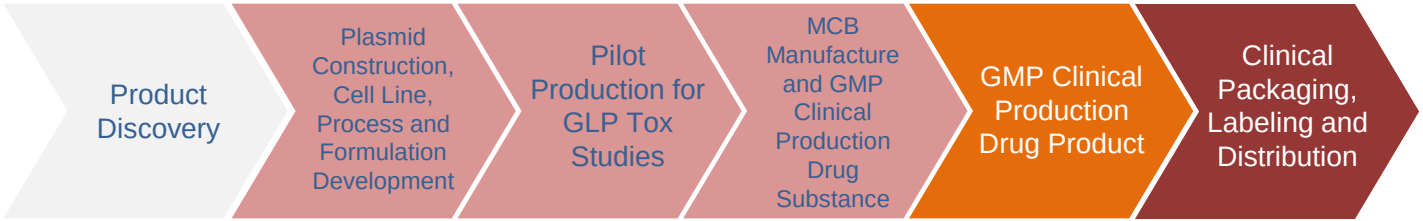


Liquid DP filled into glass vials

Formulation Development and Drug Product Stability Studies

- Developed a stable formulation for storage of DS (-20ºC)
- Developed a stable formulation for DP (2-8ºC)
  - Evaluated
    - pH
    - Excipients
  - Formulation selected based on 3-month stability data
  - Goals
    - Liquid DP formulation (10 mg/mL) for intravenous administration
    - Stable DP product for >24 months at 2-8ºC storage
    - DP is compatible with container/closure system and in-use compatibility (if DP to be diluted in IV bag)
- Key stability-indicating assays

When Did We Time Interactions with FDA?



Initiated cell line development

Pre-IND meeting-- asked CMC and tox questions; preliminary DS, DP stability

Filed IND (1 mo GMP DP stability)

Summary

- If you are a scientist at a company wishing to develop a new biologic for clinical testing, plan on outsourcing manufacturing to a competent CDMO
- A CDMO can design a production process and can provide high quality product to meet regulatory requirements in sufficient quantity
- CDMO's have particular expertise, and capabilities should be evaluated carefully
- Plan on 1-2 years to develop a cell line and process and manufacture tox and clinical product
- Plan your interactions with FDA around the uniqueness of your product
- You may want to seek a CMC consultant to assist in this effort

Questions

Steven Chamow, PhD
steve@chamowassociates.com
(650) 274-3753

Tracy Kinjerski
tracy@chamowassociates.com
(714) 600-3904

www.chamowassociates.com

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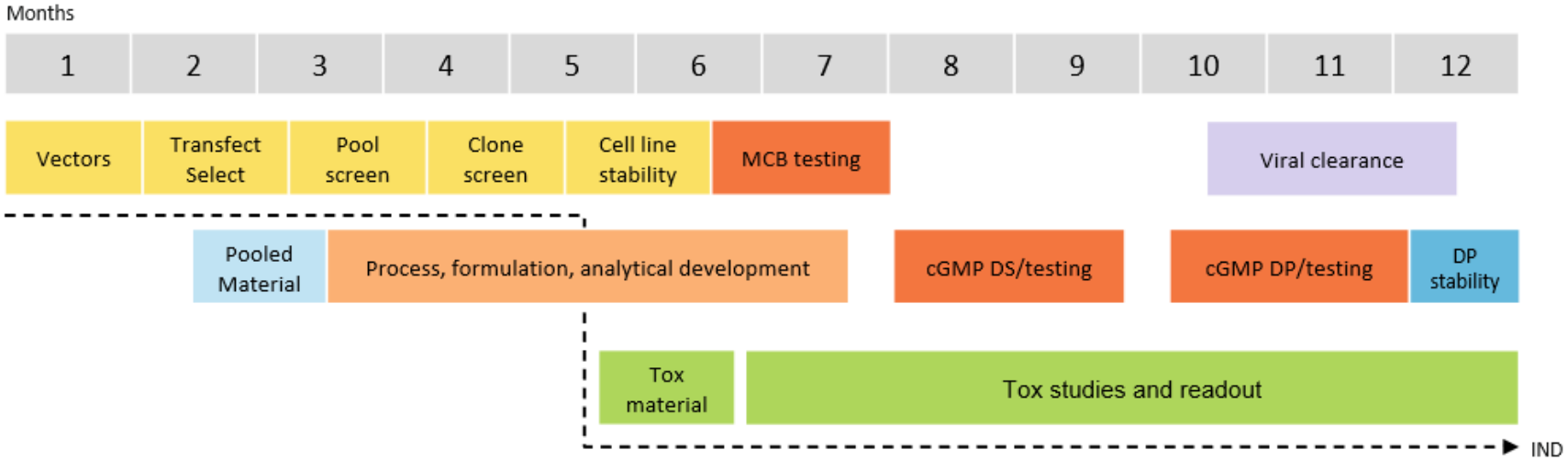
Current mAb development timeline

State-of-the-art technology applied to achieve 12 mo



---- Critical path to IND

From Kelley, *Nature Biotechnol.* **38**, 540-545 (2020)

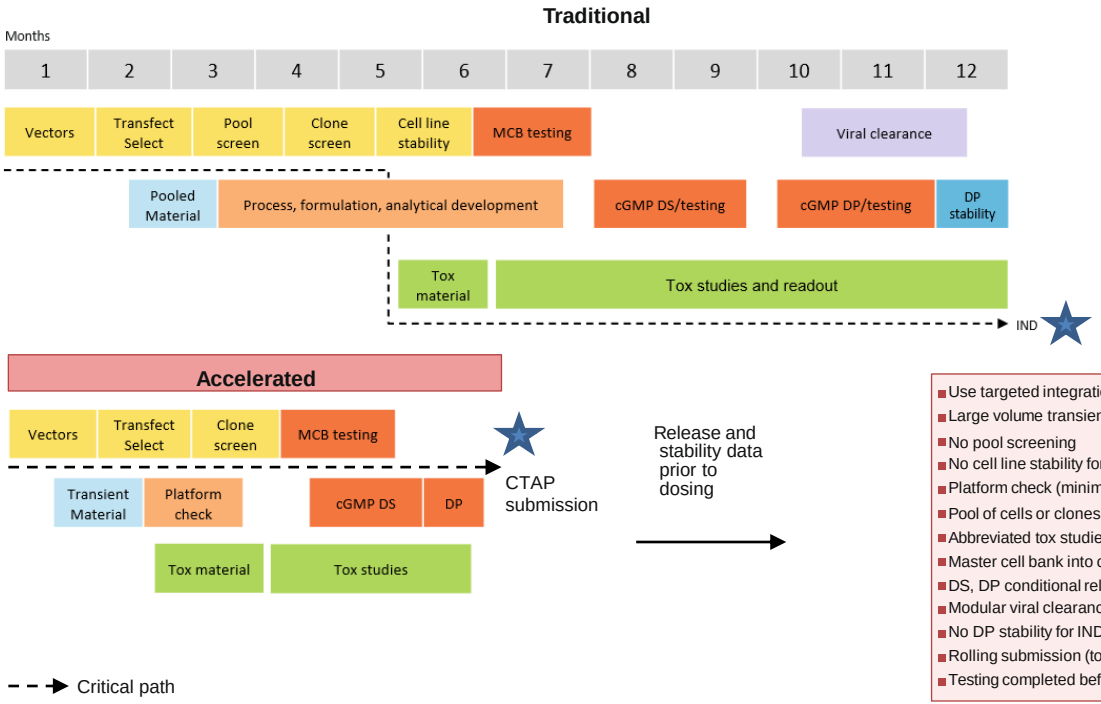
Acceleration during COVID-19

How are programs moving faster than 12 mo?

- Adopt latest technological advances
  - Highly productive cell lines
  - Large bioreactors using single-use technology
    - Enables production of thousands of doses from single batch of >5 kg
- Focus on platform approach
  - Human IgG1 expressed in CHO cells
    - Safety and quality risks are low
    - >50 have been commercialized
    - Substantial platform knowledge, cGMP production experience and facilities
- Accept higher business risk
  - Consider caveats, but…with no increased risk to patients in first clinical trials (risk/benefit)
- Why not after a pandemic?

Faster CMC development timeline for pandemic

Potential reduction from 12 mo to 6 mo



- Use targeted integration/high productivity host
- Large volume transient material supply
- No pool screening
- No cell line stability for clone selection
- Platform check (minimal PD/form/AD)
- Pool of cells or clones used for toxicology studies
- Abbreviated tox studies off critical path
- Master cell bank into cGMP production w/o testing
- DS, DP conditional release
- Modular viral clearance—no studies
- No DP stability for IND
- Rolling submission (tox, release, stability)
- Testing completed before first patient dosed

From Kelley, *Nature Biotechnol.* **38**, 540-545 (2020)

What's new here?

- Integration of innovative CMC methods with focus on speed
  - Targeted integration
  - Single round of cloning with imaging
  - Ambr15
  - Development supply run from large scale transient culture
  - Tox production from cell pool
  - No RCB--growth of production cell line concurrent with MCB manufacture
- Abbreviated tox studies
- Accepting higher business risk