"The Nuts and Bolts of Antibody Development: Accelerating Antibody Drugs to the Clinic" Workshop
Antibody Engineering & Therapeutics Conference
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The Process of CMO Selection for Antibody Development: Matching Capabilities to Need

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Overview

- The Challenge
  - Client company/project
  - Constraints
- The Match
  - Considerations for candidate CMOs
- Scope of Work
  - Development
  - GMP production
  - Timing of pre-IND meeting, IND
- Summary

The Challenge

The Client

- Client company
  - Small, venture-funded Bay Area biotechnology company
  - Internal capabilities
    - POC research laboratory
    - No CMC development infrastructure

The Project

- Client company sought to develop pre-clinical mAb for oncology
  - Product
    - Humanized IgG1
  - Hired external consulting group to execute CMC
    - Identify, evaluate and select and manage CMO
    - Develop pre-IND strategy
    - Write CMC module of IND
  - Starting point
    - *In silico* amino acid sequence
    - Target product profile

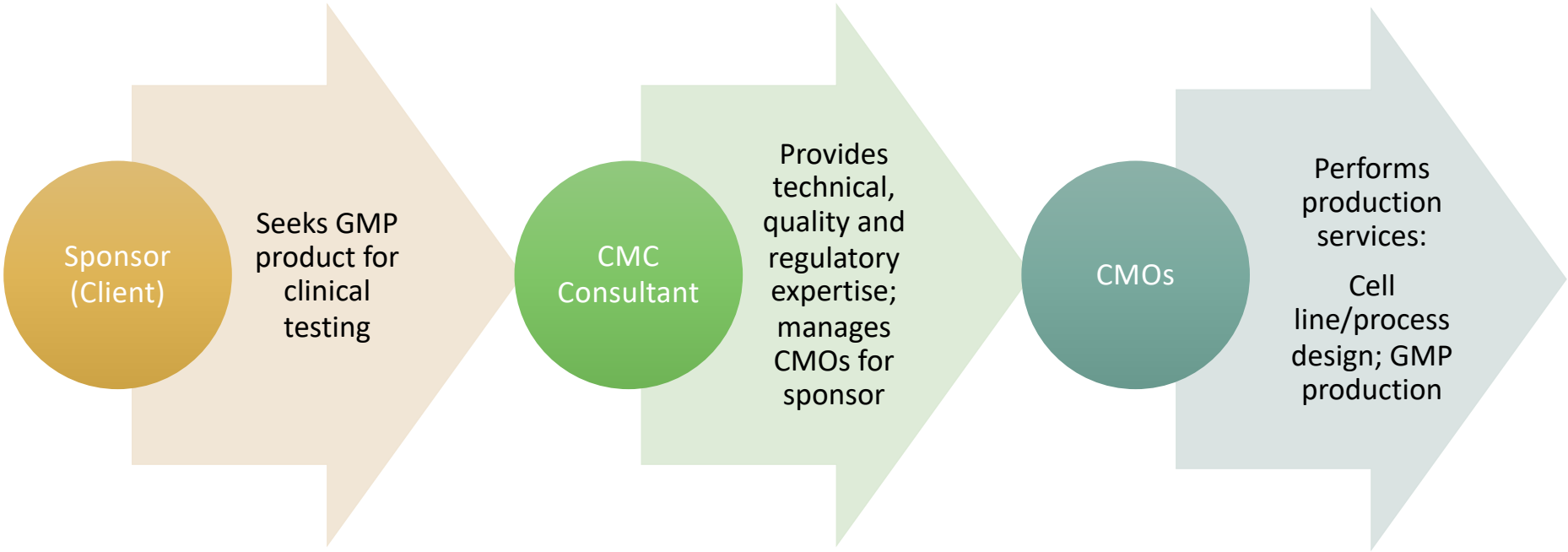
Target Product Profile (TPP)

- ”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

Based on 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

Use of CMC consultants to select and manage CMOs



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The Match

We evaluated CMOs with different capabilities and expertise

- Expertise varies
  - Enzymes
  - Cytokines
  - Growth factors
  - Monoclonal antibodies
  - Fusion proteins (Fc, albumin)
  - ADCs
- Capability varies (one-stop shop or not)

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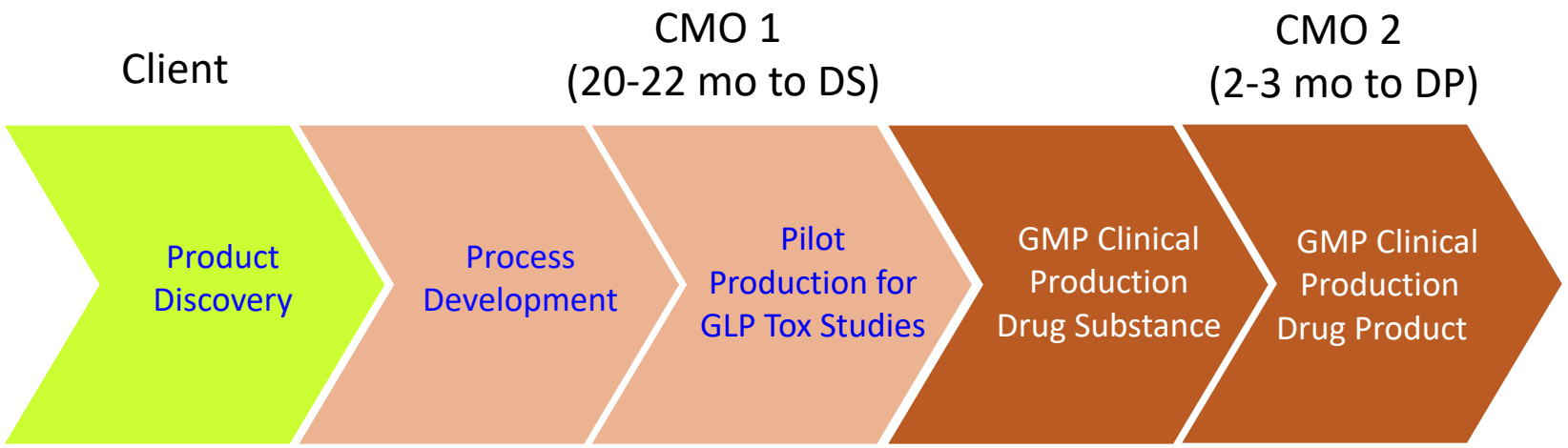
Project phases and timeline



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Factors in Matching Client to CMO

- 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

Factors (cont'd.)

- One-stop shop or different CMOs
  - Cell line development
    - Not all CMOs are equally good at making cell lines
    - Wanted a CMO with proprietary technology
  - Process development
  - Formulation development
    - This formulation was straightforward
  - Analytical methods/Stability
  - MCB—production/characterization
  - cGMP
    - DS
    - DP

Scope of Work

The starting point…
Synthesizing cDNA from an amino acid sequence

mAb γ1 Heavy Chain

Amino Acid Sequence

MAVLGLLFCLVTFPSCVLSQVQLKESGPGLVAPSQSLSITCTVSGFSLTDYGVRWIRQPPGKGLEWLGVIWGGGSTYYNSALKSRLSISKDNSKSQVFLKMNSLQTDDTAMYYCAKEKRRGYYYAMDYWGQGTSVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGKTS

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

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…to the goal

Producing bulk drug substance and filling drug product

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Scope of Work

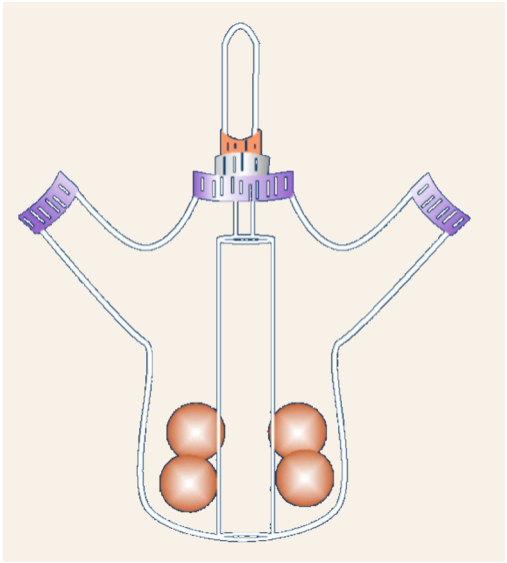
- Development
  - cDNA synthesis and vector construction
  - Cell line
    - RCB
    - MCB
  - Process
    - Upstream
    - Downstream
    - Formulation
  - Analytical
    - Compendial
    - Product-specific
      - Platform methods
      - Potency

Scope (cont'd.)

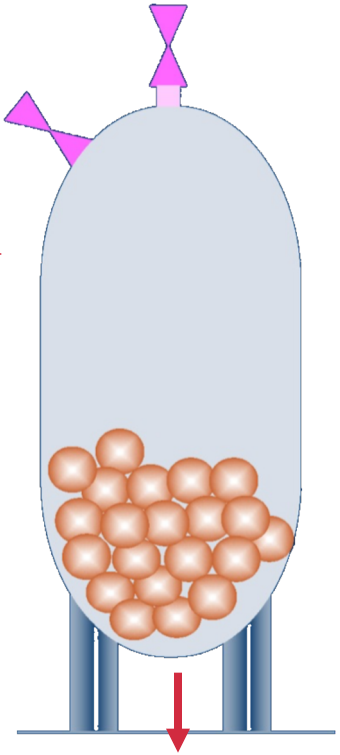
- Tox production
  - Reference material
  - Preliminary DP stability
- Characterization of reference material
- GMP production of DS
  - Viral clearance study
  - ICH Stability
- GMP production of DP
  - ICH Stability

Cell line and process development

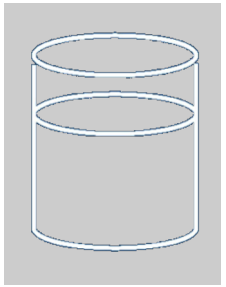
Elements of the process



Cell line



Upstream process



Downstream process

Formulation and testing

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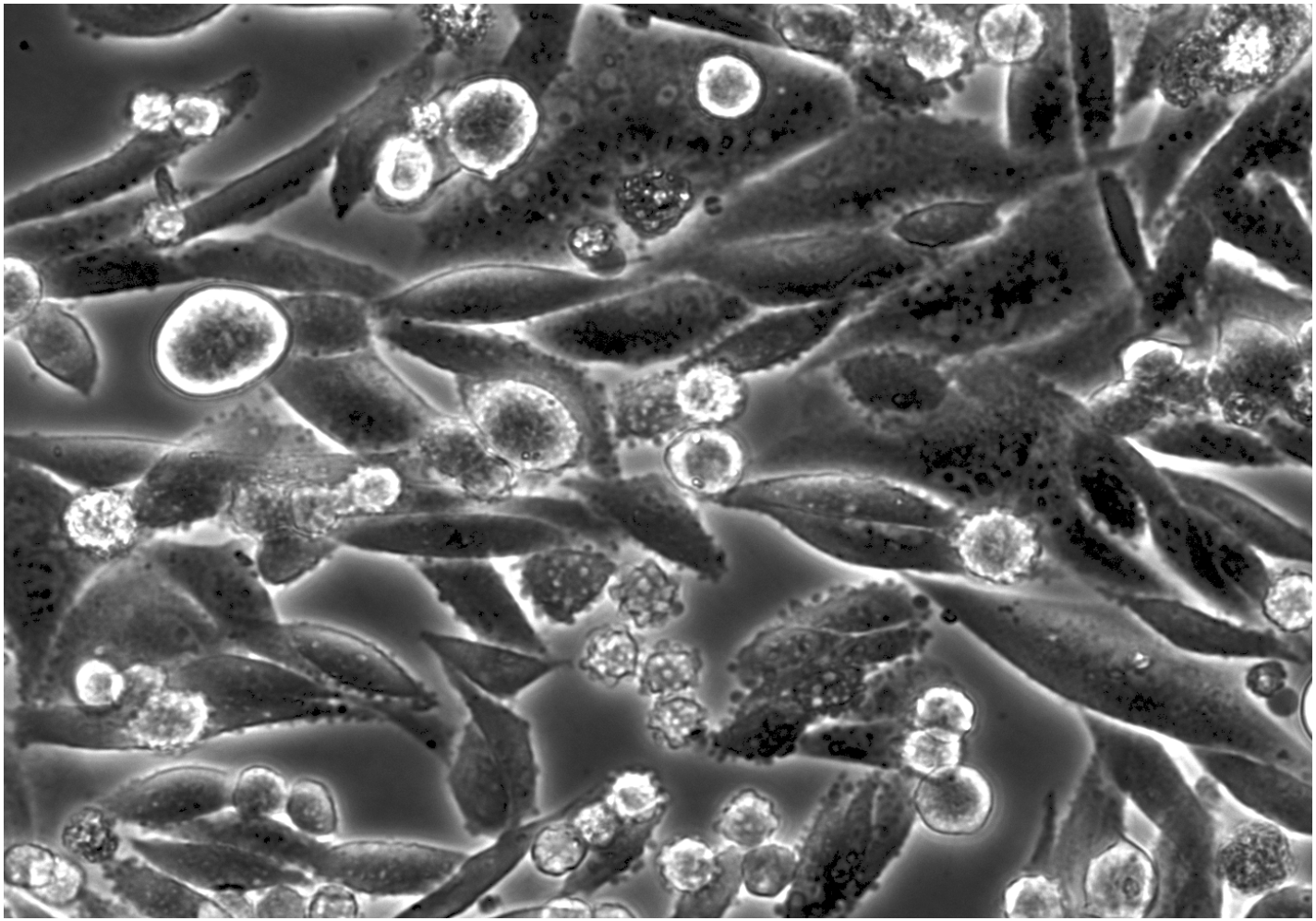
First consideration: Cell line/expression system

Type of cell line	Expected productivity	Timeline*	Cell line stability	Cost components		
				Fee for service	Milestone payments	Royalty
Proprietary (requires license)	2-5 g/L, may require proprietary media	Faster 5-7 mo aa sequence to RCB	Confirmation may not be critical path task	Yes	Yes	Yes
Non-proprietary (public domain)	1-2 g/L, generally with commercial media	7-9 mo, aa sequence to RCB	Confirmation of stability is critical path task	Yes	No	No

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

We went with Chinese hamster ovary cells/proprietary expression system



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Productivity of cell culture process

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

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

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

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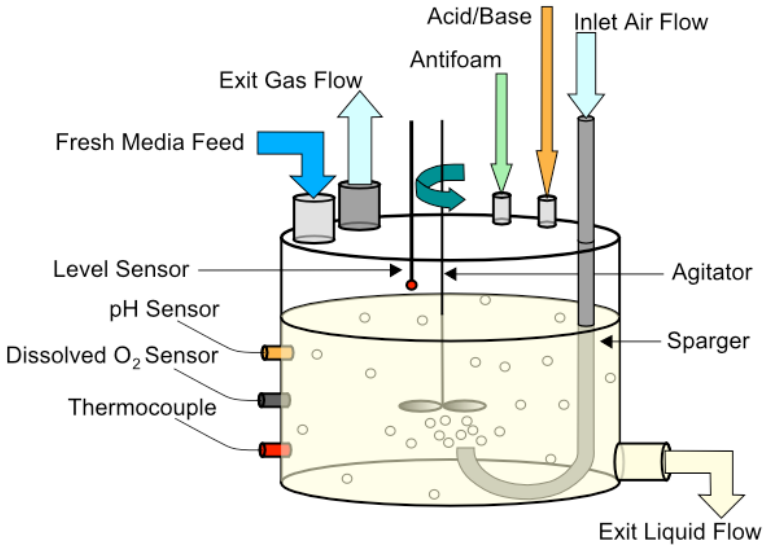
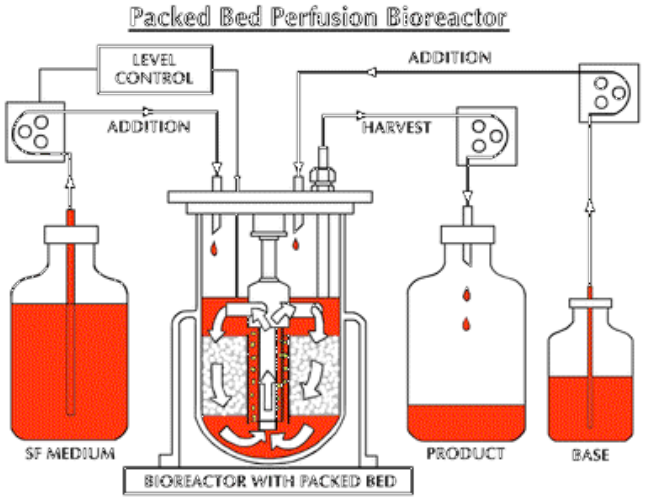
Second consideration: Cell culture process design

- Fed-batch
- Perfusion





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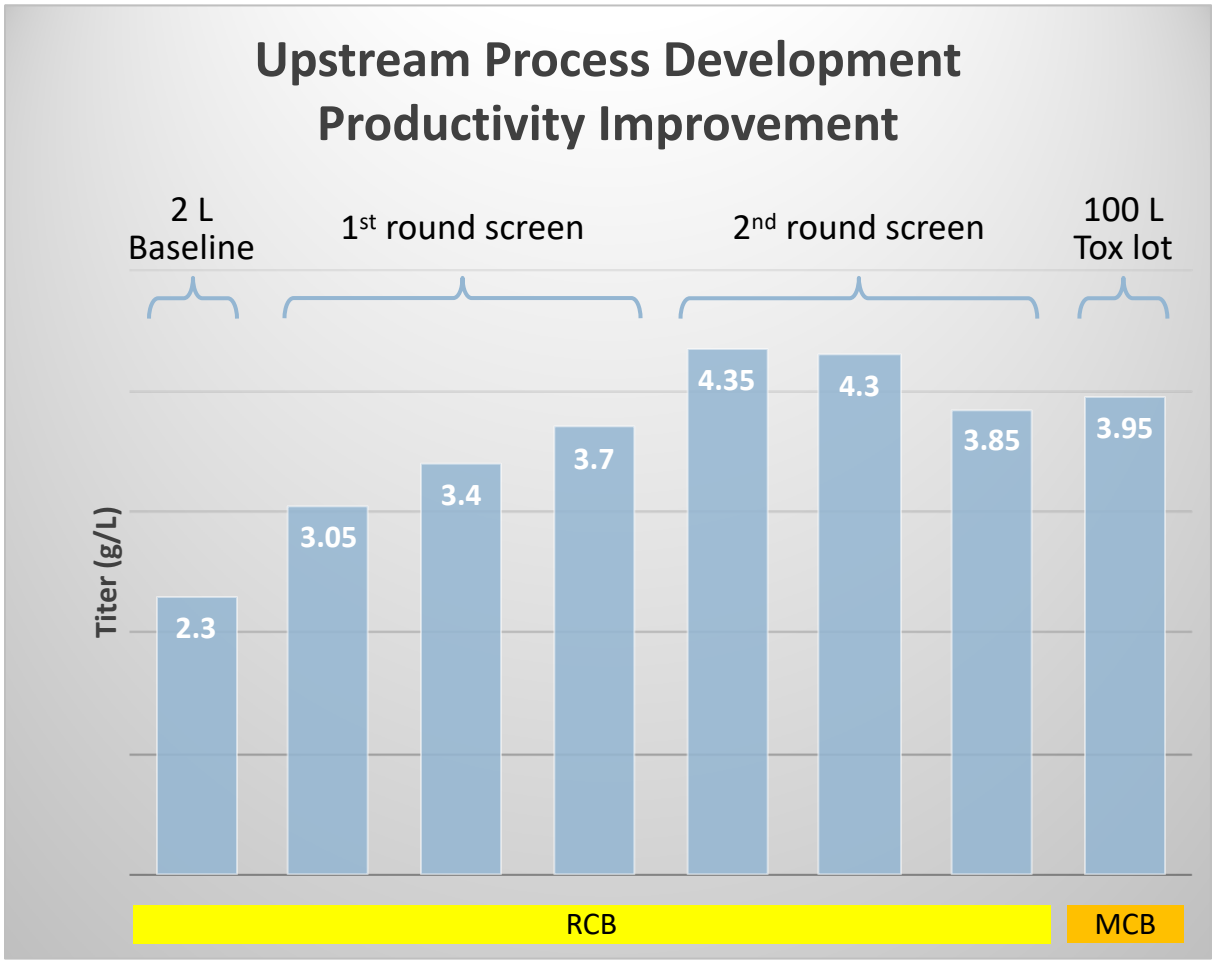
Process development runs—Product titer



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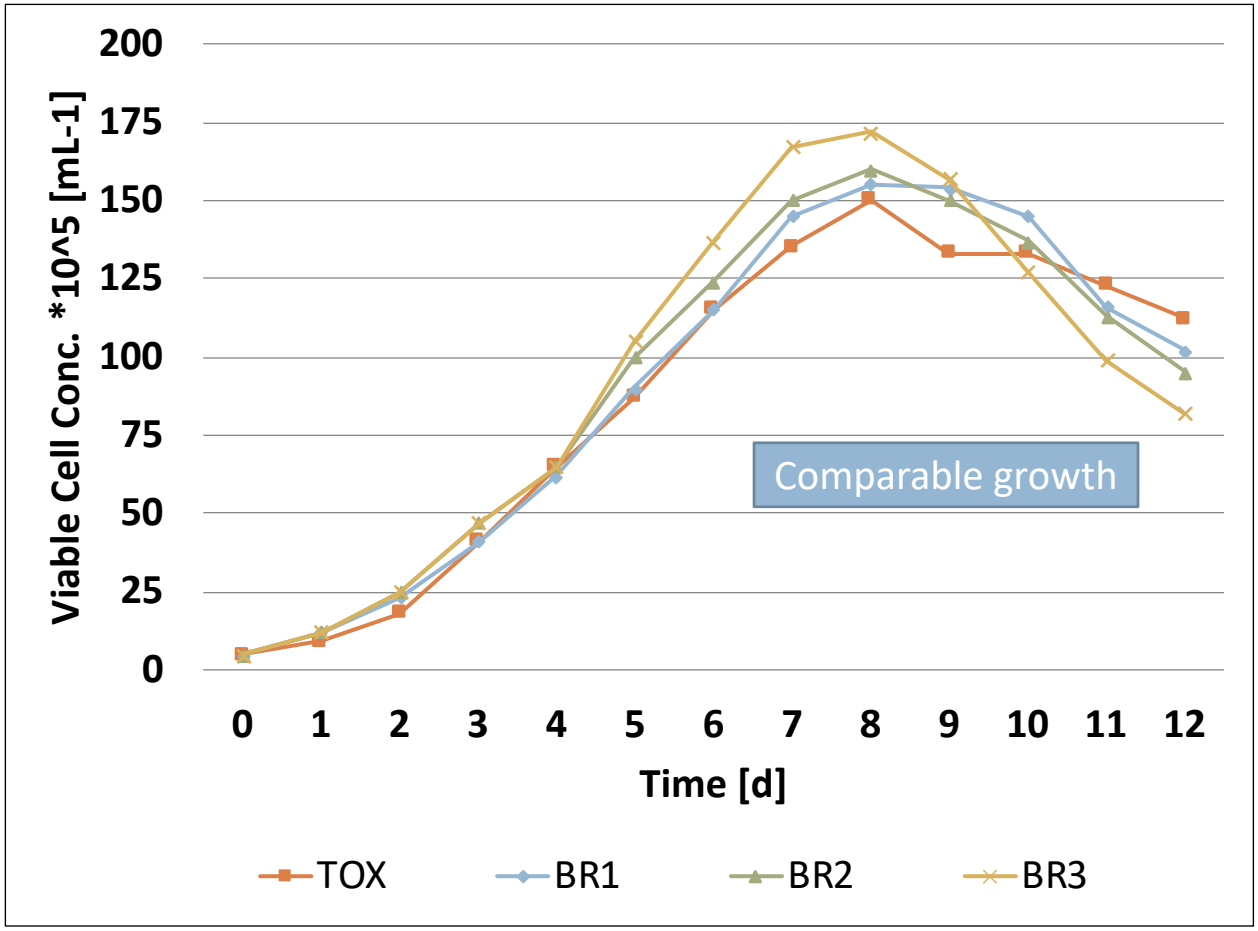
GMP Production

Scale up

- Confirmation runs at 2 L bench scale
  - Performed with RCB
  - Confirms performance of complete process
- Tox production
  - Performed with MCB
  - Intermediate scale (100 L R&D pilot)
  - Process reflects GMP process
  - Reference material
- GMP production
  - Performed with MCB
  - 2000 L
  - Samples taken for
    - Virus clearance study
    - DS, DP stability
  - Qualified assays

Tox vs. bioreactor confirmation runs – VCD



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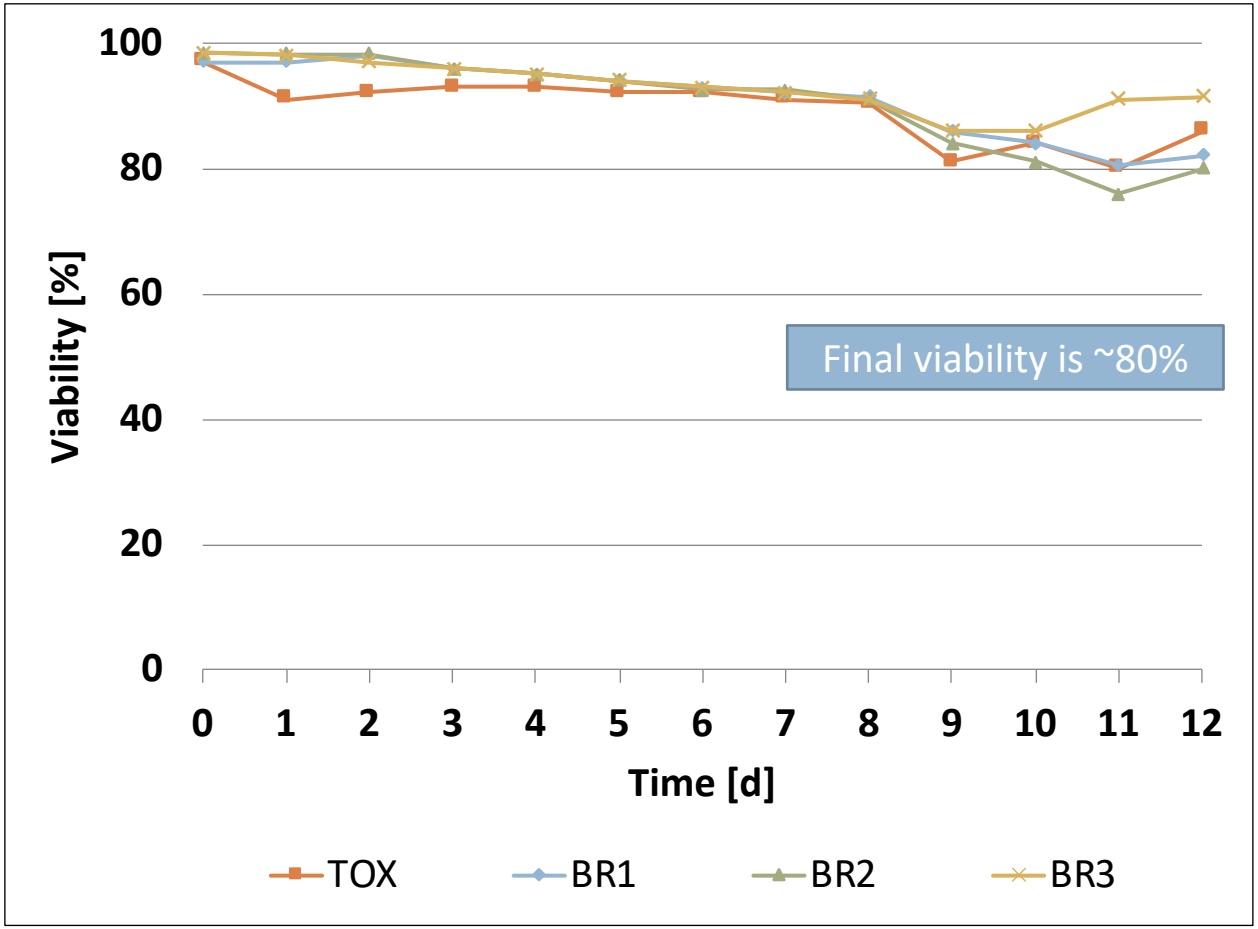
Tox vs. bioreactor confirmation runs – Viability



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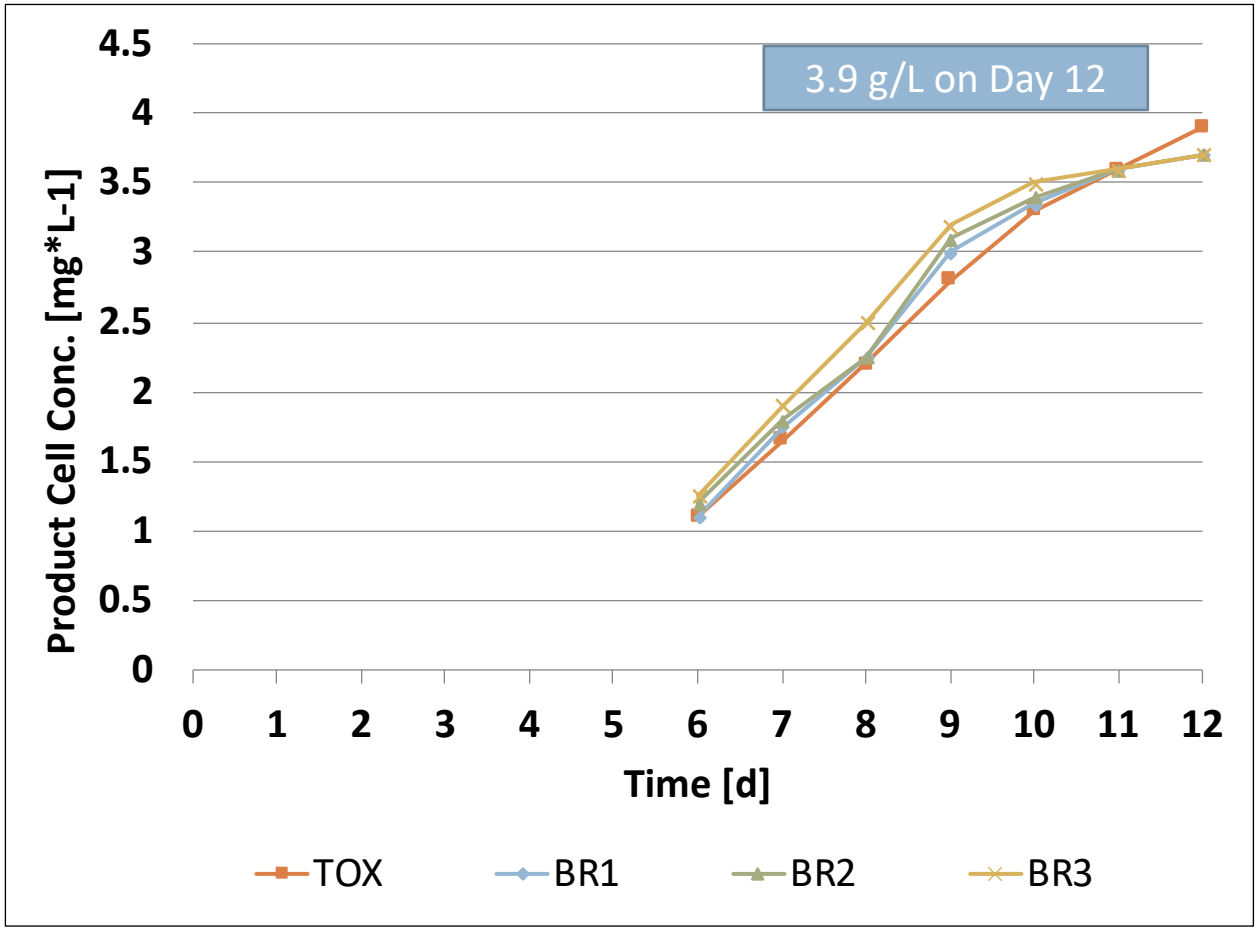
Tox vs. bioreactor confirmation runs – Titer



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Summary of process
mAb bulk drug substance (DS)

Fed-batch production

Cell Bank Vial

Seed Train

Inoculum Train

Production Culture

Centrifuge/Filtration Harvest

Protein A Chromatography

Multiple cycles per harvest

Anion-exchange Chromatography

Cation-exchange Chromatography

Virus Filtration

UF/DF

70-80% overall product yield

Frozen bulk DS

Compounding

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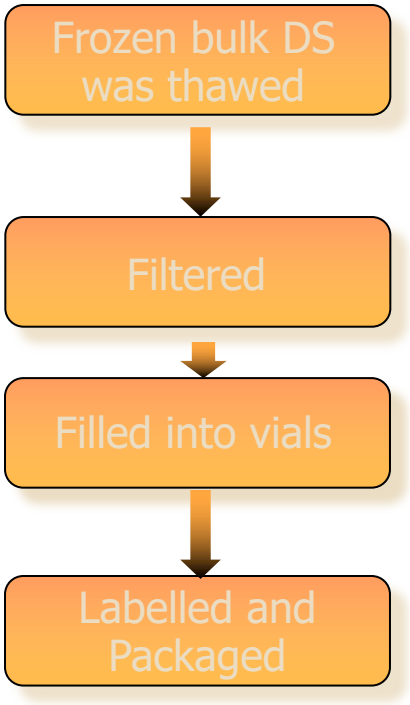
Summary of process
mAb drug product (DP)



Liquid DP filled into glass vials

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Formulation development and drug product stability studies

- Developed a stable formulation for storage of DS (-20ºC)
- Developed a stable formulation
- for DP (2-8ºC)
  - Formulation evaluation
    - 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 2-8°C storage
    - DP is compatible with container/closure system
- Key stability-indicating assays

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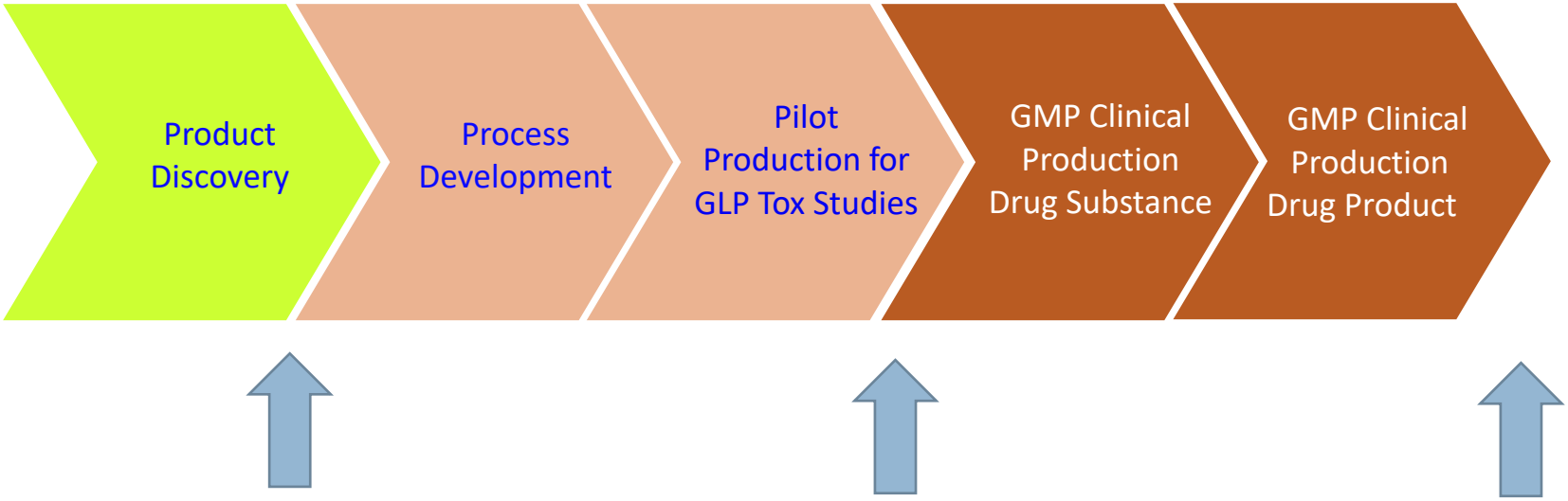
When did we time interactions with FDA?



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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 CMO
- A CMO can design a production process and can provide high quality product to meet regulatory requirements in sufficient quantity
- CMO's have particular expertise, and capabilities should be evaluated carefully
- Plan on 2 years to develop a process and manufacture clinical product
- You may want to seek a CMC consultant to assist in this effort

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