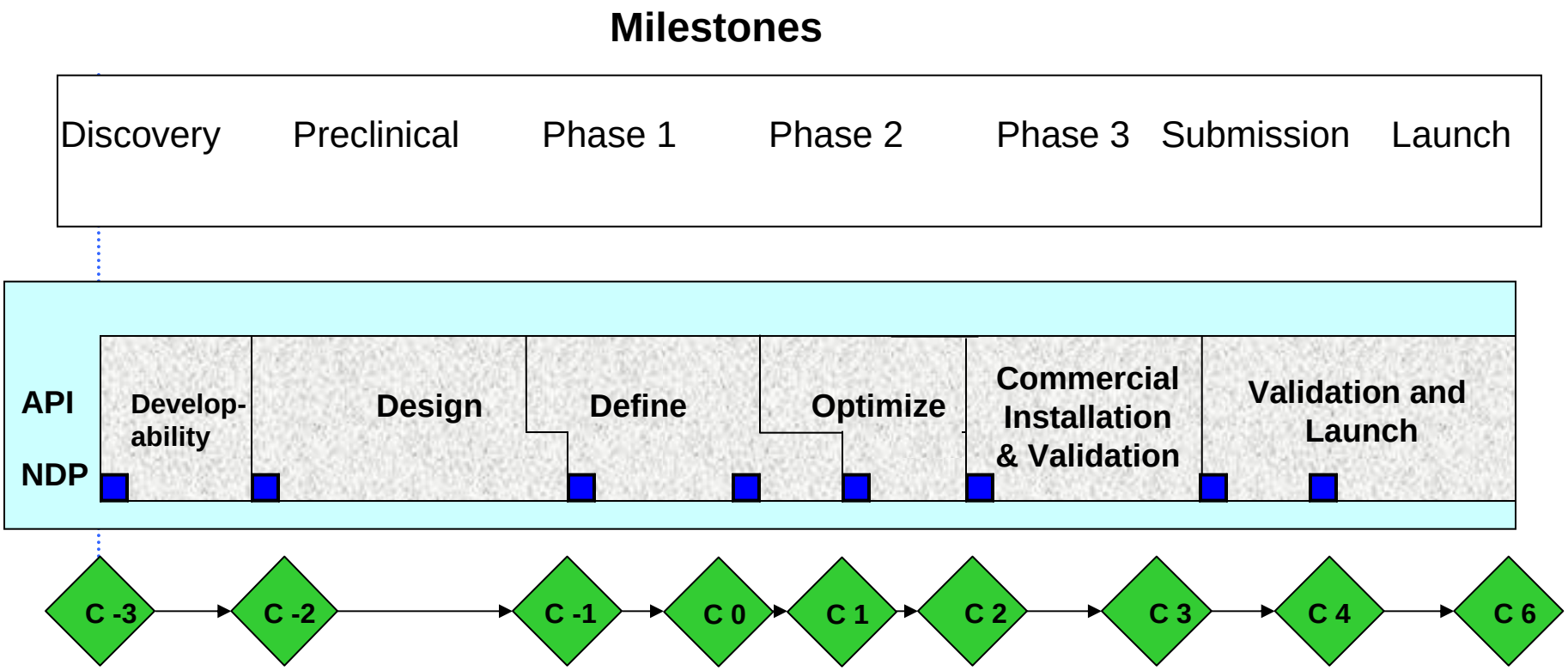
Governance

Single Process Map - Key Milestones and Stages



NOTE: Development involvement from Lead Declaration through 1+ year post launch

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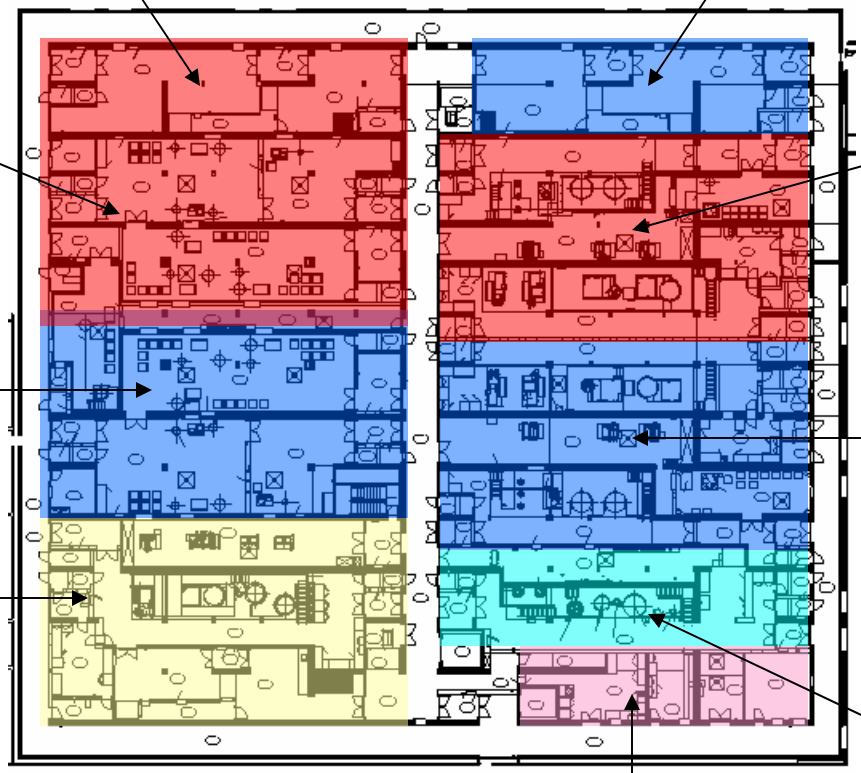
K360 Second Floor – Main Processing



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Unit Ops and Purpose

Overview

Unit operations	Purpose
Cell culture	Biosynthesis of Mab
Centrifuge/filter	Remove cells, clarify broth
Detergent Viral Inactivation	Inactivate lipid enveloped virus using Triton X-100 detergent
Protein A capture	Capture and Purify the Mab, remove MCC components, reduce HCPs, and nucleic acids
Low pH Inactivation and Neutralization	Inactivate Virus using low pH condition
CEX/AEX, ion exchange chromatography	Further purification and reduction of HCP, polymer, leached Protein A, and DNA
FNL polishing chrom – ion exchange or mixed mode	Further purification and reduction of HCP, leached Protein A, nucleic acids and soluble aggregate
Viral Nanofiltration	Removal of viral particles
TFF	Buffer exchange, concentrate
Final API Fill	Dispense final bulk API into containers

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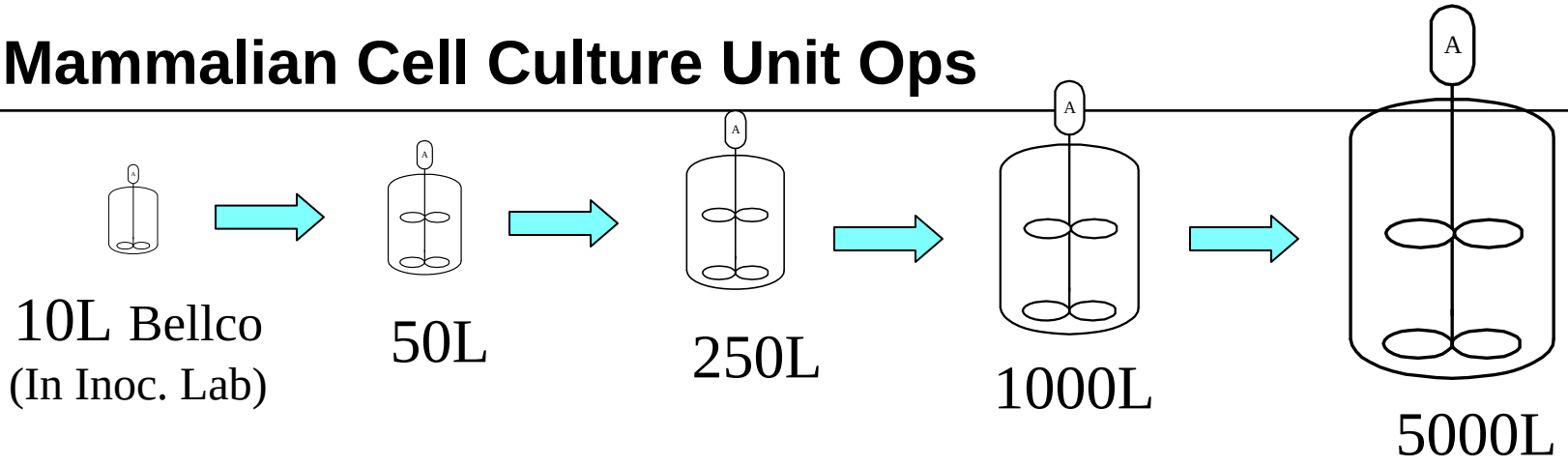
Upstream Operations

Mammalian Cell Culture Unit Ops



Braun Reactor Capabilities:

- Automated CIP and SIP
- 3 Addition ports with scales (Antifoam, Caustic, Nutrients)
- Temperature control with Steam and 0° Glycol
- Sparge and Overlay Gas flow control with Back-pressure control (Air, Oxygen, CO_2 and Nitrogen)
- pH, DO_2 probes with control
- Variable speed agitation with dual A100 marine prop impellors
- Harvest capabilities on the 1000L and 5000L

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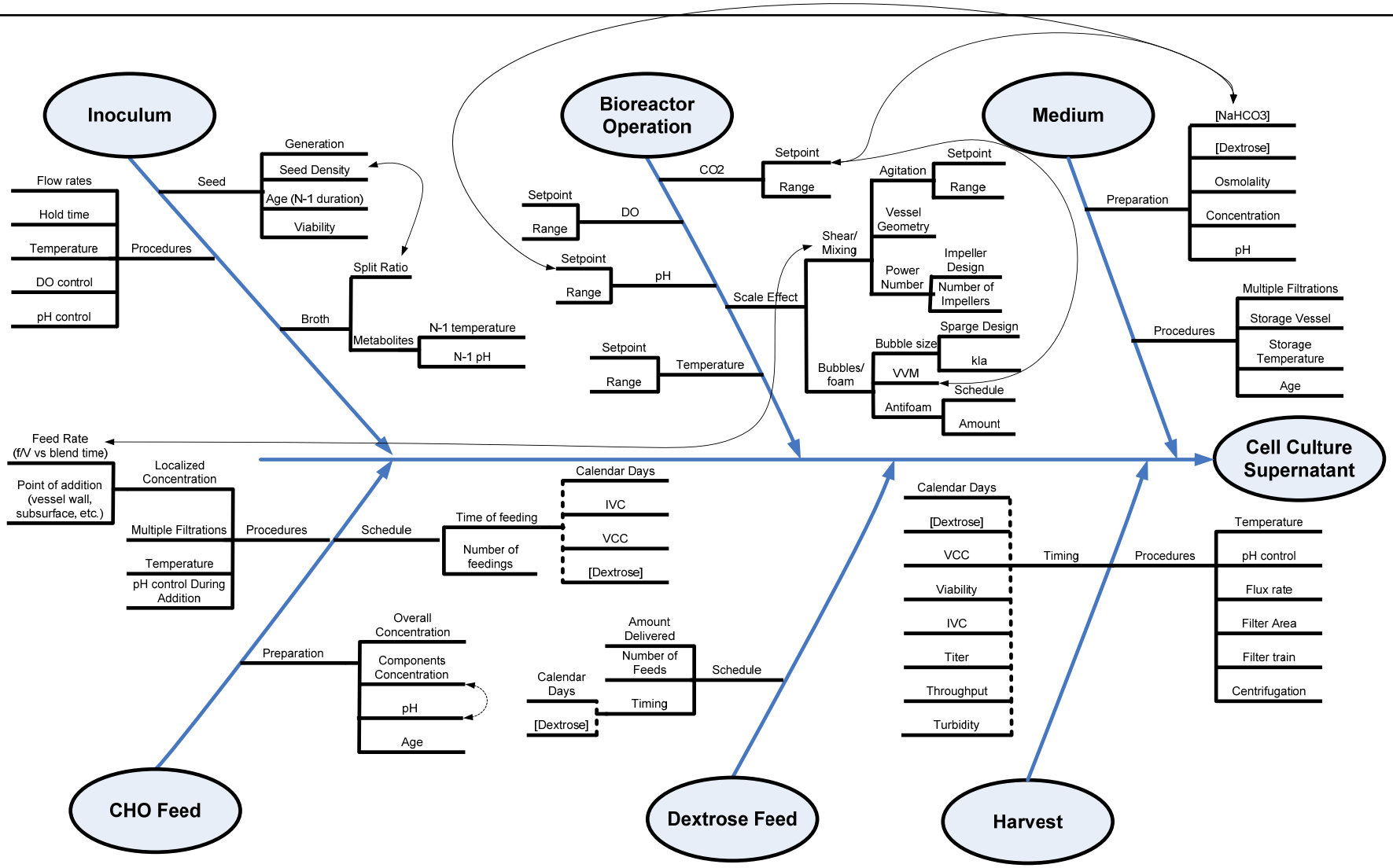
Fishbone diagram

Mammalian Cell Culture Process Flow – DOE Guide



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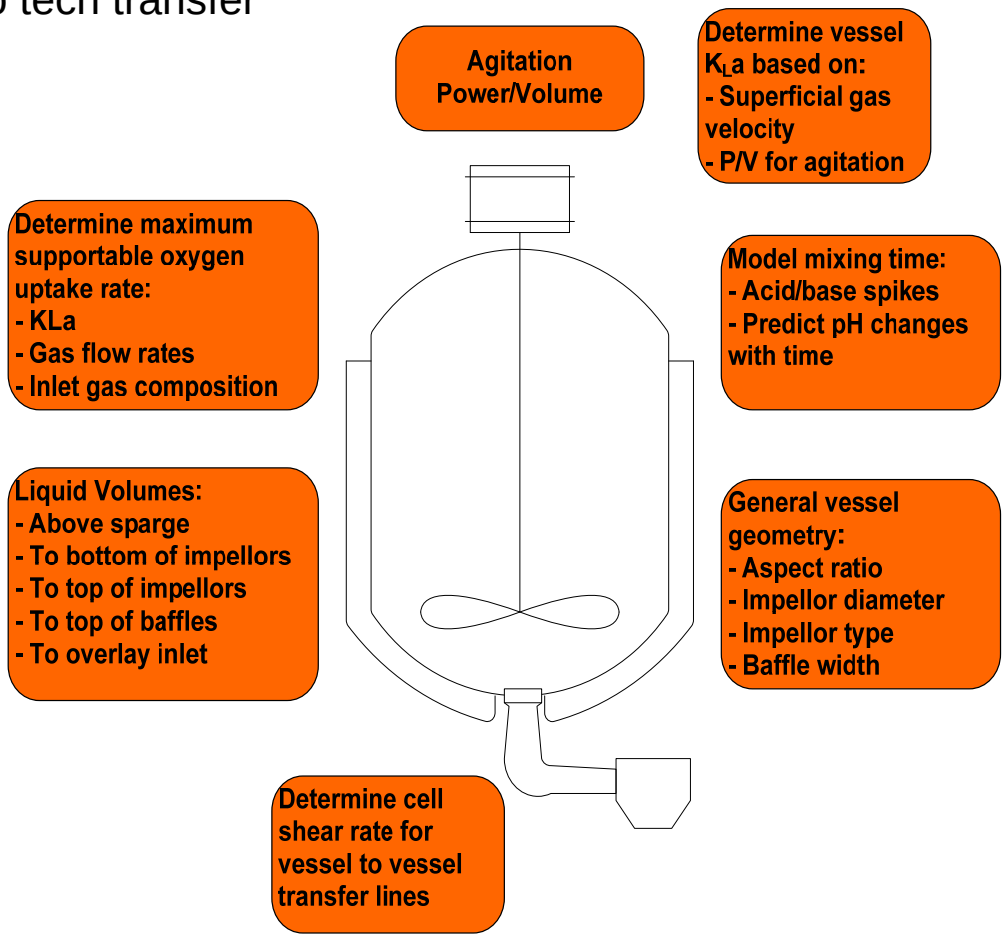
Bioreactor Characterization and Operation

Leveraging Assessment for All Processes

The capability to optimally mix and support O2 and CO2 levels must be demonstrated prior to tech transfer



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Downstream Operations

Purification and Filtration Unit Ops

3 Rooms per Suite

Room	Chrom I	Chrom II	TFF Area
Process Area (ft^2)	1400	1100	700
Portable Equipment Stations	3	2	1
Laminar Flow Hoods	0	0	1

Portable skids and support equipment



Use of Disposables







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Purification

Focus on More Rapid Turnaround

Portable Equipment Benefits

Clean and move out of processing suite or move to cleaning area makes area staging and turnaround simpler

Disposable Product Contact Surfaces

Disposable bags in reusable carts require no product-to-product cleaning verification

Area turnaround has shortened from weeks to 1-2 days

Platform Impact

Risk assessment analysis for bags, tubing, etc can be leveraged across processes (leachables data and vendor choices)

Avoid design or alternation of fixed steel equipment for each process

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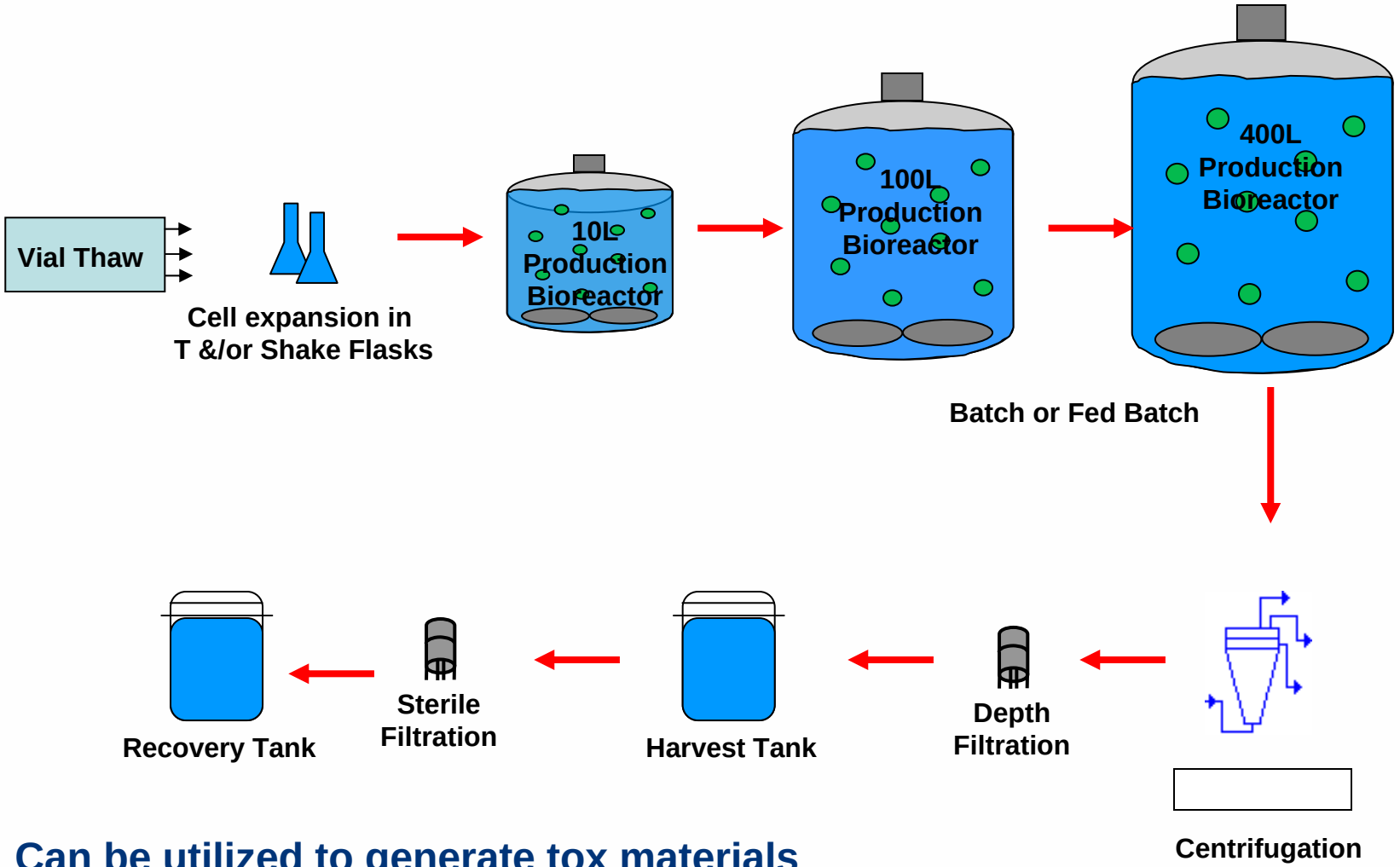
Lab Scale Development Reactors (n=30)



Scale-up Model Development Reactor (400 liter)



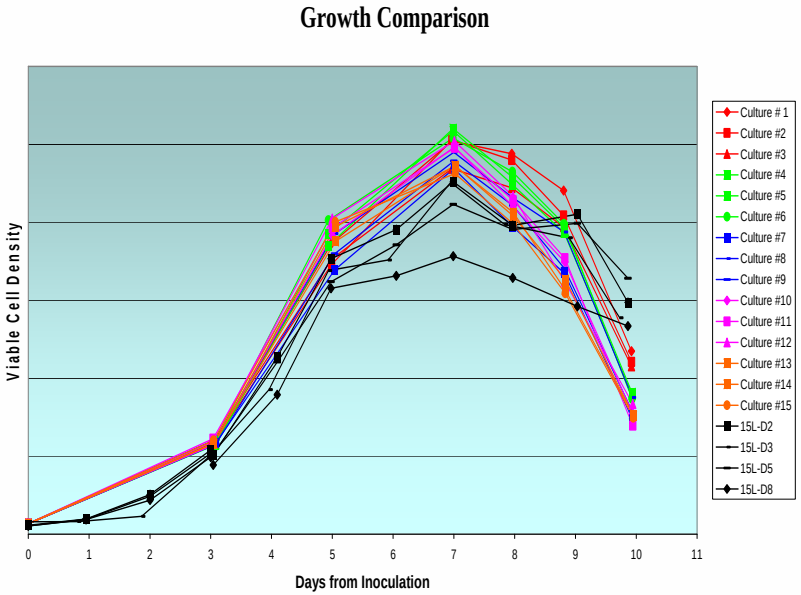
Cell Culture Process Platform

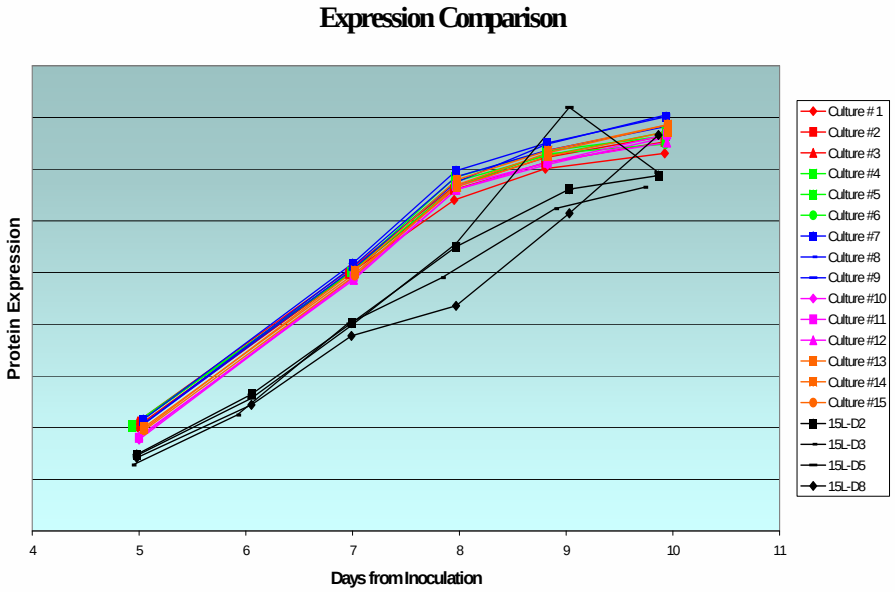


Can be utilized to generate tox materials

Project A Phase 3 - *MTM Results*

- **Develop an acceptable shaker scale-down model**
  - **Provide a bioreactor model that supports high cell densities**
  - **Increase capacity for screening experimental conditions**





Outline

Wyeth's FIH Development Platform

- High level messages
- Business drivers
- Design concepts
- Design criteria
- Asset optimization
- Platform elements and the integrated platform
- Implementation benefits
- Observations

Key Concepts Influencing the Platform Design

- Platform must ensure predictability of process performance and product quality
- Platform schedule must be achievable and sustainable
- Process and product must be capable of *reasonably* meeting CTM demand and worldwide regulatory requirements and expectations
  - Product quality
  - Cell line productivity and stability
  - Toxicology and Phase 1/2 clinical material demand
- From the start, prefer to have a cell line that has the capability to support a product launch

Key Criteria Influencing the Platform Design

- CHO K1 host cell
- Clonal cell line
- Titer >1 g/L
- Qp >10 pg/cell/day
- Growth rate = 0.023 – 0.033 h-1
- 12-day fed batch production
- Standard, completely defined medium (inoc. buildup, seed brx, prod brx, feed composition)
- Standard cell thaw strategy
- Standard equipment
- In process hold points
- Two column purification process
- Overall process yields 50% - 80%
- DS confirmation runs in pilot prior to FS
- Toxicology material from pilot
- Standard tech transfer documentation
- DS production duration of <3 months
- Standard sampling plan
- Templated batch and formulation records
- Standard bulk fill and membrane strategy
- Standard Bill of Materials
- Standard 2 wk change-over strategy
- Standard formulation excipients
- Standard container closure
- Lyophilized dosage form
- Common approach for DS/DP release testing

Assets to Optimize…People and Organization

People and Organization

- Experienced staff
- Responsible for Phase 0 through Phase 3 drug substance and drug product development and commercial process and product improvements
- All development functions and facilities are co-located at a single site

Assets to Optimize…Facilities

Production Facilities

- Cell bank suite
  - ~ 2,000 sq. ft. plus additional cell bank storage areas
  - Dedicated HVAC with controlled pressure, temperature and humidity
  - Simultaneous, *multi-product* capacity
- Clinical drug substance facility
  - 38,000 sq. ft. clean manufacturing, multi product
  - Bioreactor hall (6000 L; 2 x 2500 L; 1 x 500 L
  - Production support (media prep, buffer prep, glassware)
  - Simultaneous, *multi-product* capacity
- Clinical drug product facility
  - Aseptic clinical drug product manufacture
  - Liquid, lyophilized vials and pre-filled syringes
  - Typical batch sizes up to 10,000 units
- DS Pilot Lab
  - 2 x 500 L; 190 L; 160 L bioreactors
  - Moderate scale purification
  - Non-GMP

Assets to Optimize…Technology

- Cell line development
  - Vector construction and transfections
  - Clone selection/screening
  - Cell line and cell bank medium development
  - WCB and MCB
  - Genotypic characterization and stability
- Bioreactor process development
  - Medium development/feeds
  - Inoculum conditions (pH, temperature, sparging, feeds…)
  - Production conditions (pH, temperature, sparging, density, duration, feeds…)
  - Harvest/clarification
- Purification process development
  - Column selection and operations (resins, geometries, buffer selection…)
  - In process hold points
  - DS storage conditions
- Analytical development
  - DS and DP release and stability methods
  - Characterization methods
- Formulation and dosage form development
  - pH, excipients
  - Freeze/thaw, shaking
  - Stability
  - Container/closure
  - Lyo cycle development
- Operations within the DS and DP production facilities

Assets to Optimize…Business Processes

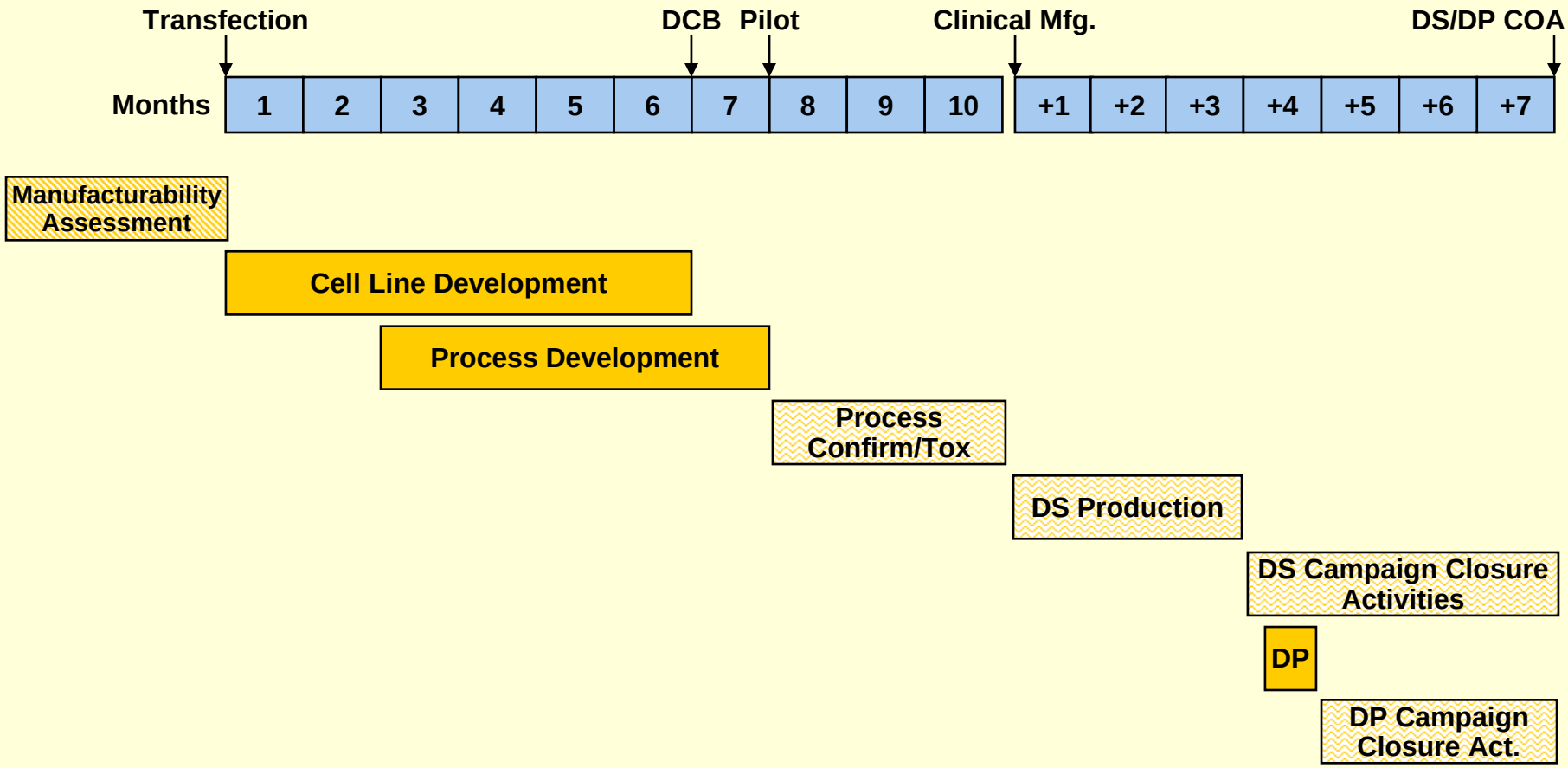
- Development project management functions
- DS and DP commitment management process
- DS and DP release/disposition process
- Technology transfer process
- Batch Record creation/review
- Investigation/Development Discrepancy process
- Platform change control
- Other quality system processes

Functional Area and Business Platform Elements are Integrated to Form a Composite

Platform elements and business processes provide definition for activities, interdependencies, schedules, etc.

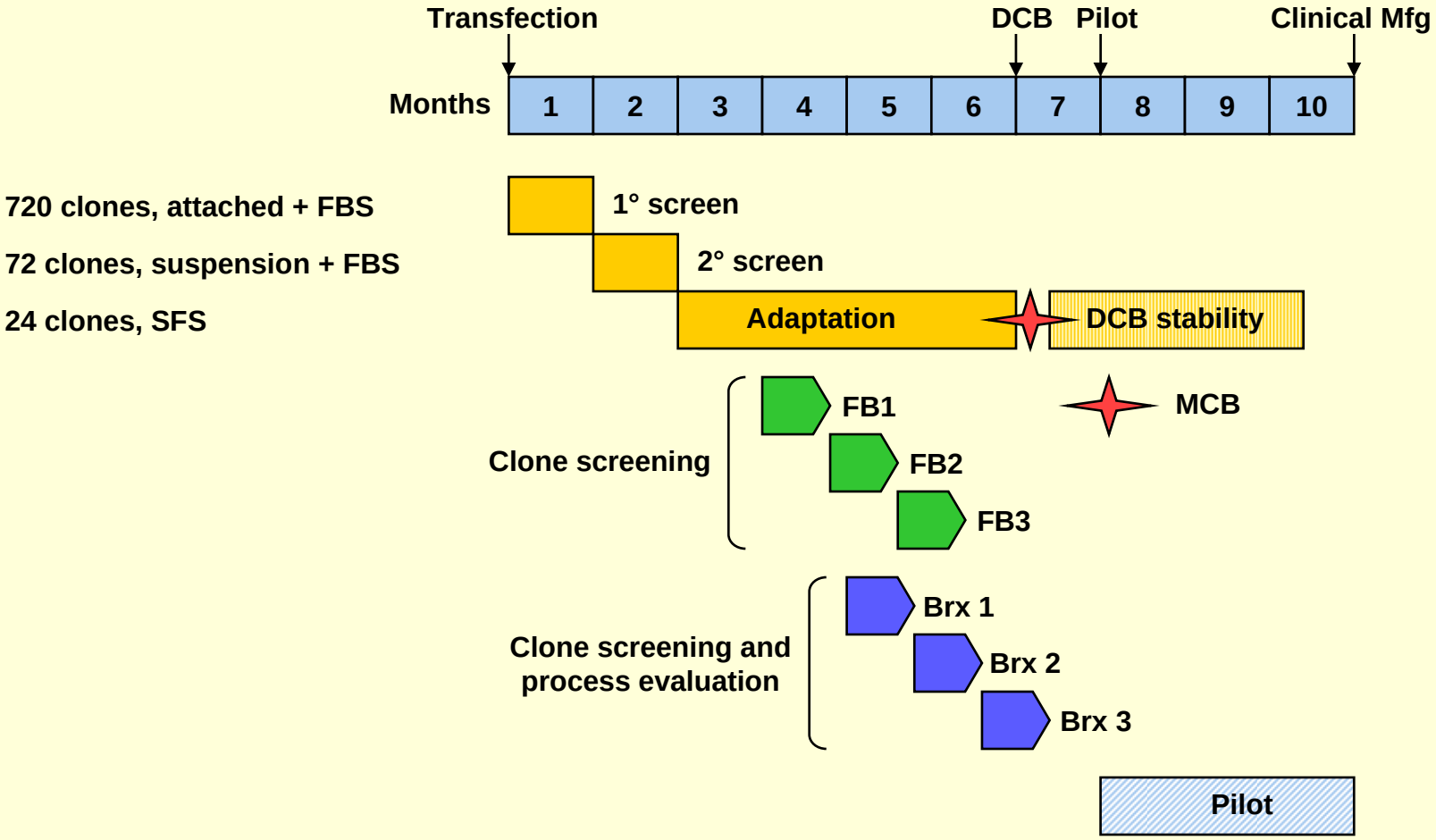
- Manufacturability assessment
- Cell line development
- Bioreactor process development
- Purification process development
- DS Pilot lab
- DS clinical manufacturing
- Formulation development
- DP clinical manufacturing
- Technology transfer
- Analytical testing
- DS and DP disposition

Critical Path of Integrated Platform Activities



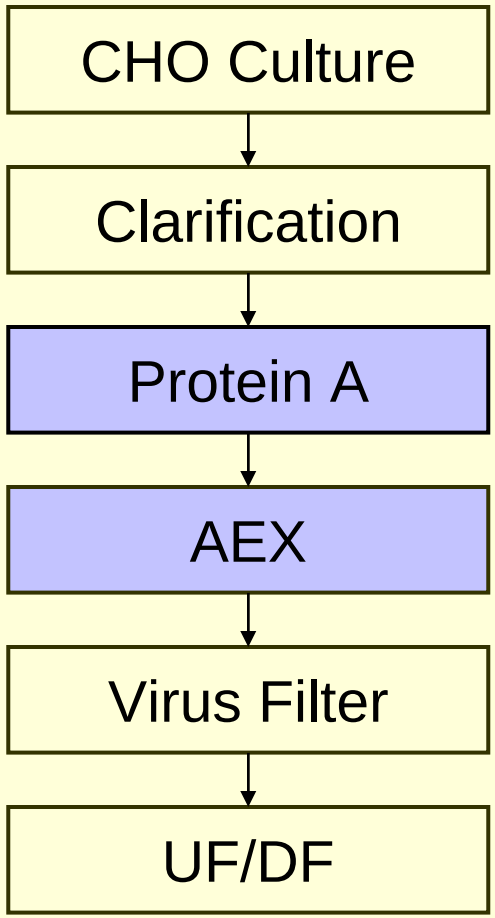
Wyeth BioPharma

Platform Delivers Cell Lines Capable of Supporting a Commercial Launch



Wyeth BioPharma

A 2-Column Purification Platform Supports High Titer Cell Culture Processes



1-4 gm/L titer, > 10^7cells/mL

Centrifugation

Single polishing step

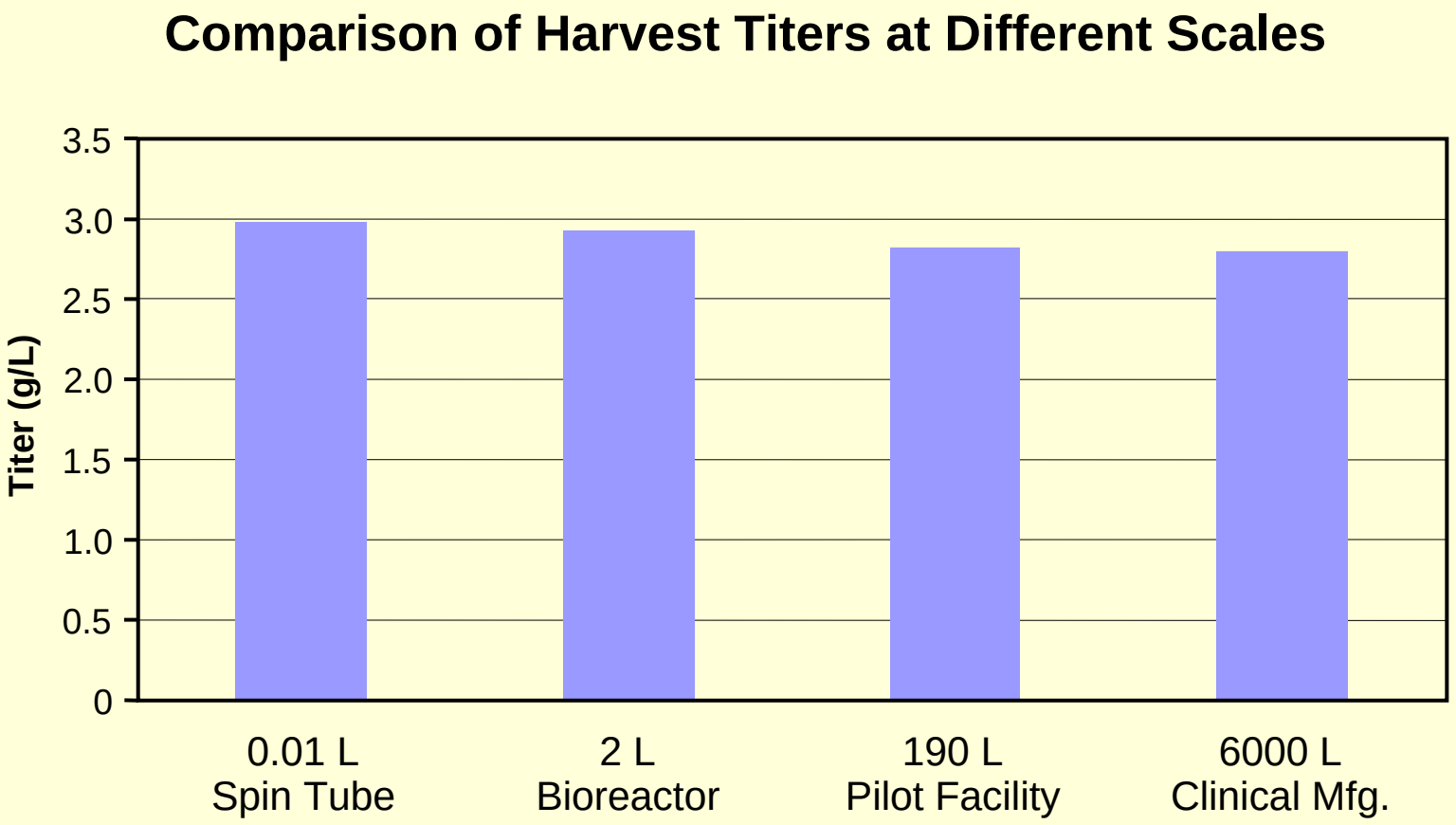
Assurance of viral safety

High concentration DS (> 50 mg/mL)

Success in Achieving Platform Deliverables

Project	ADF Line	Batch	Titer (g/L)	Yield (Kg)
mAb 1	2500 L	1	1.71	2.45
		2	1.81	2.52
mAb 2	6000 L	1	2.80	10.9
		2	2.60	10.1
mAb 3	2500 L	1	1.26	2.08
		2	1.28	1.91
Novel Scaffold	6000 L	1	1.80	2.28
		2	2.28	3.30
		3	2.13	3.00

Spin Tubes are Predictive of Clone Performance at Larger Scales



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How Do We Implement Changes to the Platform?

- New technology is generally identified by a team having the functional area ownership of that technology
- New technologies are developed and tested off platform
- Technology is often compared head to head with current Platform method
- Changes to the Platform must be endorsed by a governance group