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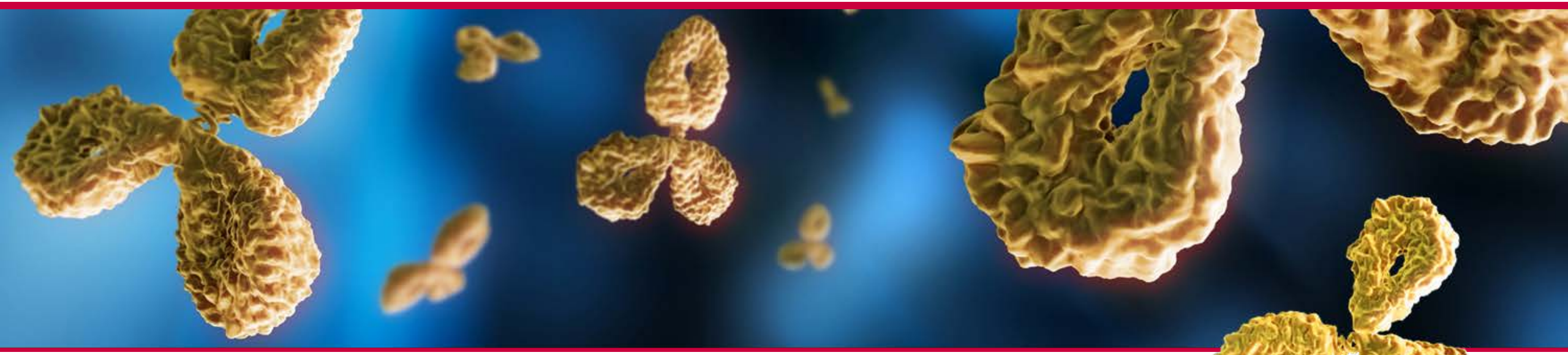

Early Stage Process Considerations for Late Stage Success

Richard Richieri
Chief Operations Officer
Avid Bioservices Inc.

Tuesday, December 3rd , 2019

Avid Bioservices Background

Avid Bioservices

Established Track Record as a Clinical & Commercial Biologics CDMO

26 Years of experience developing in-house product & technology

26 Years of biologics manufacturing experience

18 Approved manufacturer of products marketed in 18 countries

15 Years of successful inspection history

14 Years of cGMP commercial manufacturing

11 Years of with single-use technology, multiple platforms

10 Successful process validation campaigns

6 Successful pre-approval inspections

0 483 FDA observations over the last 4 audits

FDA U.S. FOOD & DRUG ADMINISTRATION

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Health Canada

Paul-Ehrlich-Institut

Australian Government
Department of Health

Republic of Turkey
Ministry of Health

ANVISA
Agência Nacional de Vigilância Sanitária

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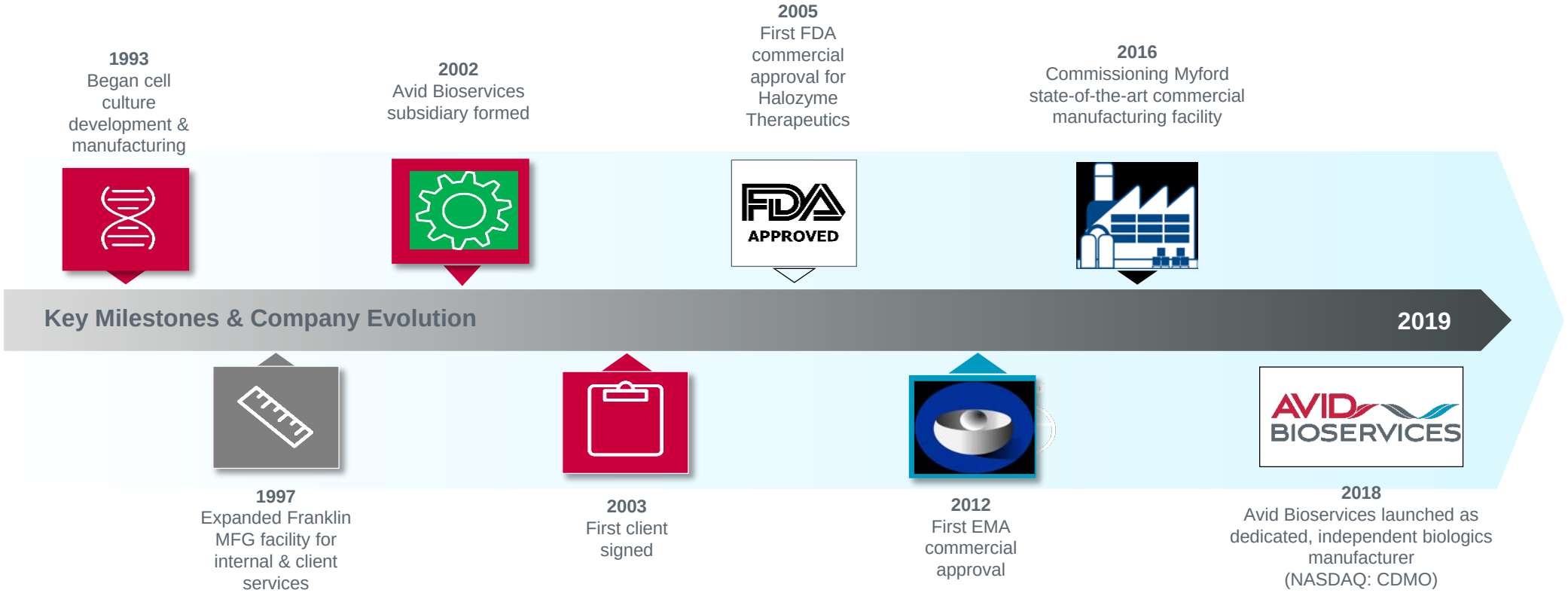
Over 26 Years of Biologics Development & Manufacturing Experience

Full-Service Dedicated Biologics CDMO Focused on Development and CGMP Manufacture of Biopharmaceuticals Derived from Mammalian Cell Culture



1993
Began cell culture development & manufacturing

1997
Expanded Franklin MFG facility for internal & client services

2002
Avid Bioservices subsidiary formed

2003
First client signed

2005
First FDA commercial approval for Halozyme Therapeutics

2012
First EMA commercial approval

2016
Commissioning Myford state-of-the-art commercial manufacturing facility

2018
Avid Bioservices launched as dedicated, independent biologics manufacturer (NASDAQ: CDMO)

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Avid Bioservices
Campus Overview

Conveniently Located on One Campus

- Located in Orange County, California (Tustin)
- 210 employees:
  - 174 operational
  - 36 SG&A
- 158,000 ft^2 campus includes:
  - Two cGMP manufacturing facilities
  - Avid's headquarters
  - Quality control facility
  - Process development facility

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CDMOs are an Important Partner to the Biopharmaceutical Industry

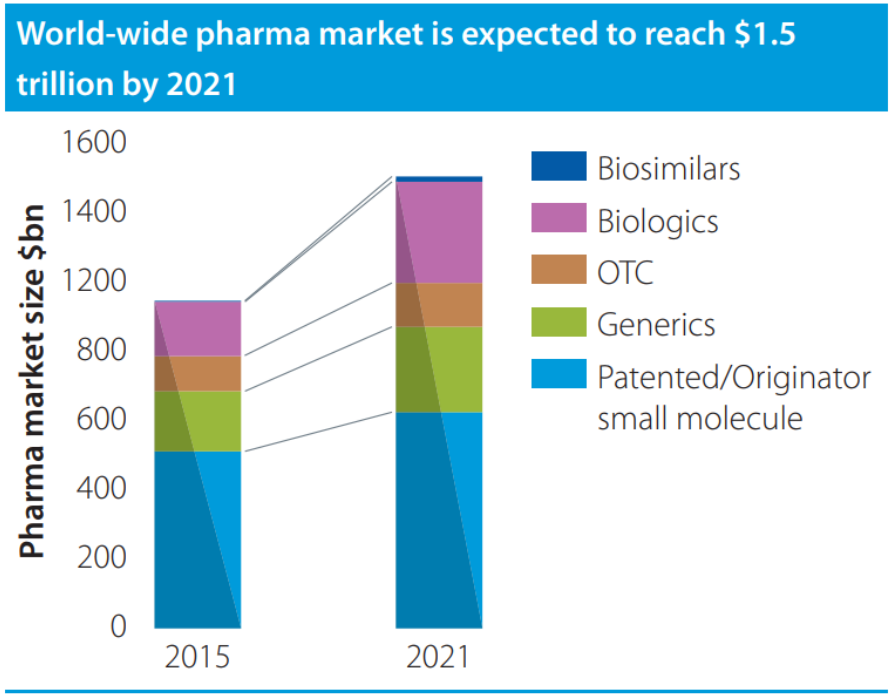

Figure 1 *Global pharmaceutical market 2015-2021*

- In particular, a CDMO that has the quality systems and scale to take a project from early phase to commercial is a significant advantage
  - ➢ Shorter timelines (Important for Fast Track)
  - ➢ Process knowledge
  - ➢ Eliminate site-to-site comparison studies

A CDMO helps to advance products from development to manufacturing and eventually the commercialization stage

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Avid Bioservices
Full Service Capabilities & Strengths

Preclinical, Clinical and Commercial Solutions

Development, Analytical & Manufacturing Services

Exceptional Regulatory Track Record

Areas of Differentiation	
Industry-Leading Regulatory Track Record	Strong regulatory compliance with *global* agencies, commercially compliant
Flexible Manufacturing and Development	Multiple manufacturing platforms offer flexibility enabling rapid responses to dynamic production processes
Cost Effective and Timeliness	Single use bioreactor technologies enhance manufacturing efficiency by reducing facility footprint
Collaborative Approach	Strong project management team providing streamlined communication and collaboration between various stakeholders; experience in-house product development background

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Current Capacity at Our Two CGMP Manufacturing Facilities

Franklin Facility (Mix of Stainless and Single Use

- Facility commissioned in 1993
- ~12,000 sq. ft.
- Full supporting utilities & infrastructure
- FDA licensed for commercial manufacture

Single Use	Stainless
1 x 1,000L	1 x 1,000L
1 x 200L	1 x 300L
	1 x 100L

Myford Current Facility “Myford North” (All Single Use)

3 x 2,000L

2 x 1,000L

4 x 200L

- State-of-the-art facility commissioned 2016
- Modular cleanroom technology
- ~42,000 sq. ft. equipped
  - Includes utilities, QC labs, warehouse

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Commercial Scale

Overview

Capacity

Myford 1 Facility

- 42,000 ft² facility, commissioned in 2016
- Integrated QC labs for in-process samples, final release, & environmental monitoring

3 x 2,000L

2 x 1,000L

4 x 200L

Myford 2 Expansion

- Next Slide

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Trusted Partner. Quality Solutions. Reliable Results.

End-to End Solutions

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Future Additional Capacity at Myford Facility

- In the same building as “Myford North” CGMP facility, we plan to > double our current capacity by building out new upstream and downstream cleanrooms
- This new processing area is called “Myford South”
- One option is shown below, but larger single use bioreactors (3kL-6kL) are also under consideration
- Currently partnering with leading A&E firm to finalize conceptual floor plan
- Detailed engineering and expansion to commence in 2020

Myford Expansion Facility “Myford South” (All Single Use)

6 x 2,000L

4 x 200L

2 x 25L (wave)

- Room for expansion: ~42,000 sq. ft.
- Multiple Purification Trains to match upstream

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Laboratory Expansion in Process Development - Upstream Development Expansion

- Located in Tustin, CA with over 6,000 ft^2 of upstream & downstream development and pilot production area
- Modern laboratory space with centralized utilities and modular space plan
- 24 x bench-top bioreactor controllers for process development & characterization
- 3 – 15 L single-use and glass bioreactor vessels for process development
- 50 – 200 L single use pilot bioreactors for scale-up and Pharm/Tox supply.

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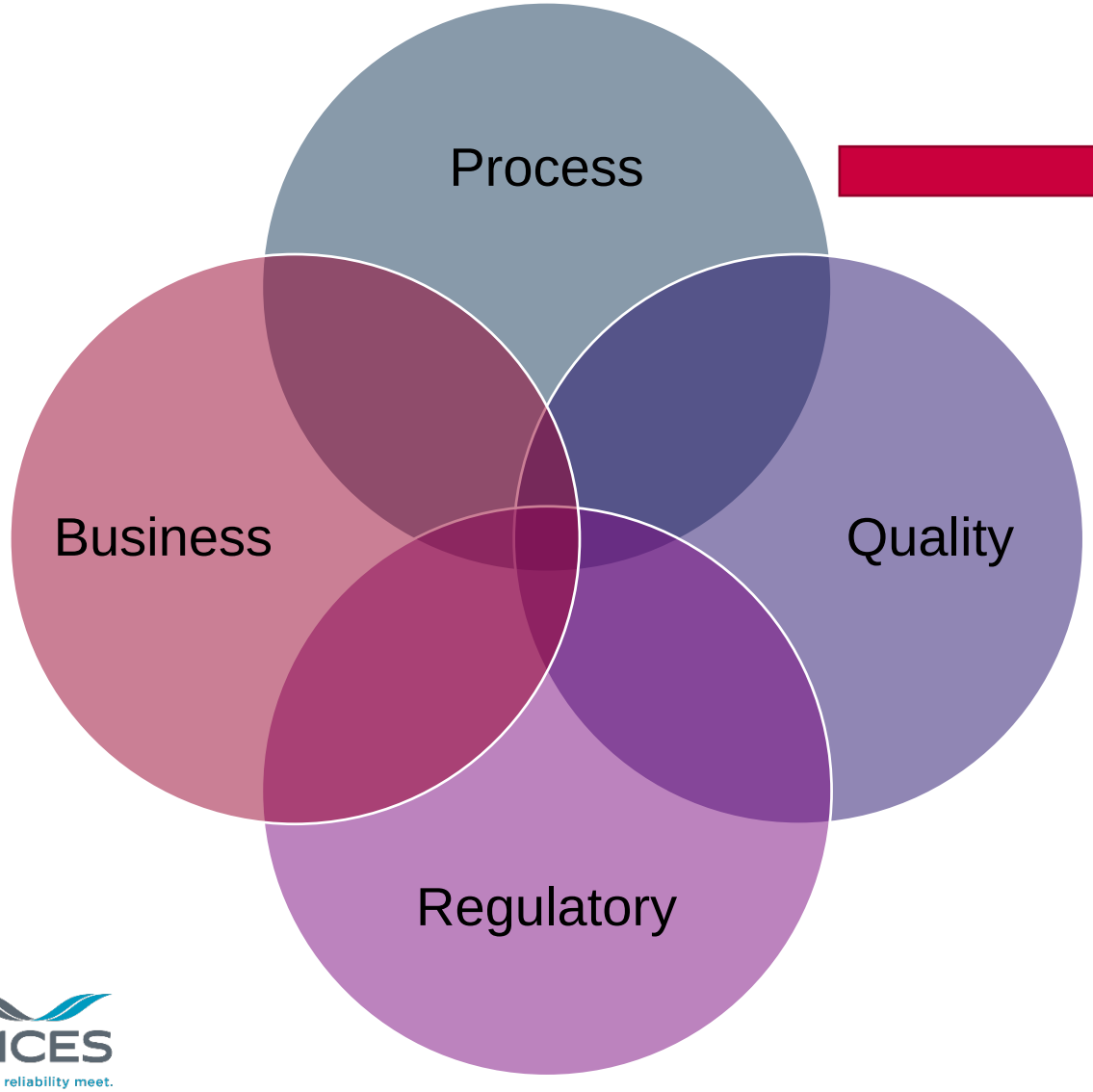
Early Stage Process Considerations for Late Stage Success

Early Process Decisions are a Driver for Success



Early stage process choices will significantly impact product quality, regulatory timelines and program costs

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Example of 2,000L Upstream Process at Avid

Some cell lines are shear sensitive in the Wave

5:1 Turndown Ratio

Cell densities are requiring large # of filters

Ensure ability to keep cold and aerated

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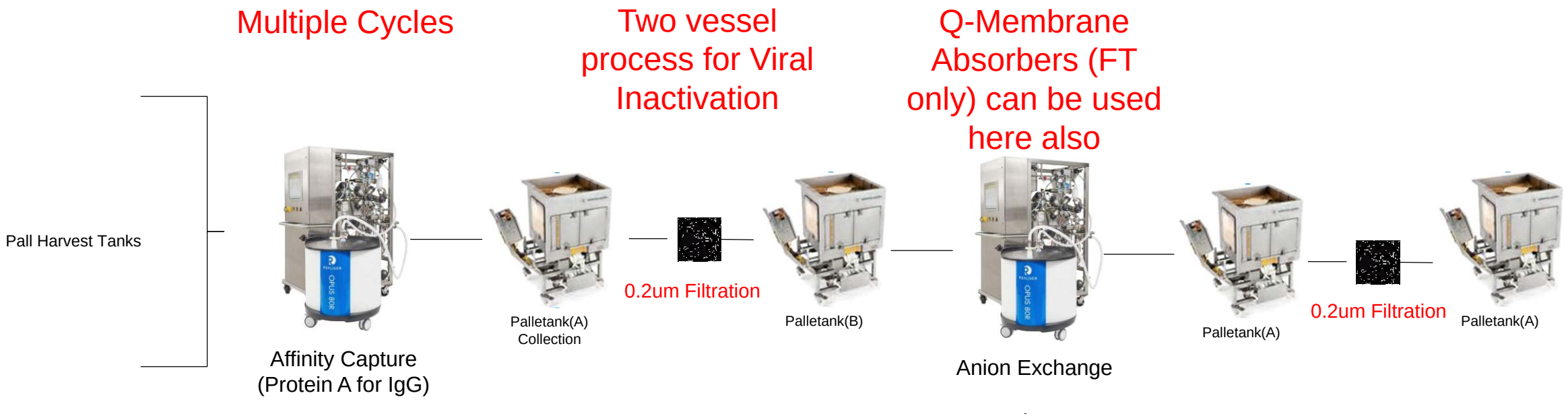
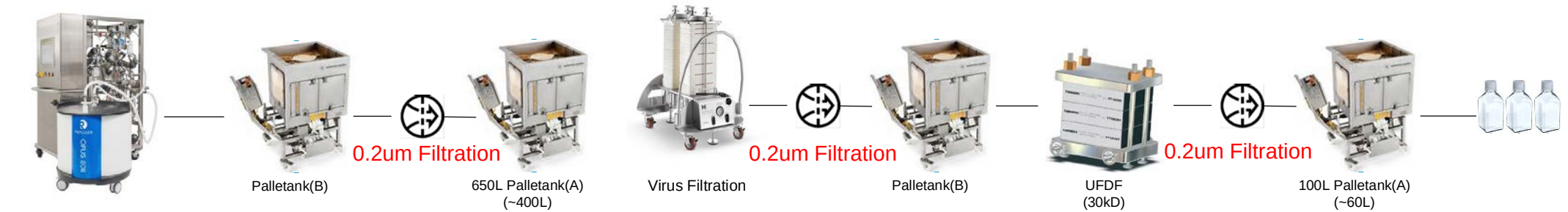
Example of 2,000L Downstream Process at Avid (1 of 2)



Example of 2,000L Downstream Process at Avid (2 of 2)

Ok to start with gradient, but for PV use step elution

Significant performance variations between vendors, need to screen!



Cation Exchange

Palletank(B)

650L Palletank(A) (~400L)

Virus Filtration

Palletank(B)

UFDF (30kD)

100L Palletank(A) (~60L)

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Process Validation

Controlled process to assure consistent drug quality

According to the FDA's 2011 Process Validation (PV) guidance, "Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process."

Phase I/II (Pre-optimized)
Optimized prior to PQ

Process Design and Characterization

- Manufacturing process is defined during this stage and is based on knowledge acquired through development and scale-up activities

Phase III

Process Qualification @ Scale

- Process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Post Approval

Continued Process Verification

- Ongoing assurance during manufacturing that the process is controlled and the outcome predictable.

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Process Validation

Controlled process to assure consistent drug quality

Ideal to “Lock in”
- MCB/media
- Final DP formulation
- Unit Operations

Phase I/II Pre-optimized

Process Design

- Manufacturing process is defined during this stage and is based on knowledge acquired through development and scale-up activities

Ideal to “Lock in”
- Process Parameters
- ID of CPP
- Effect of Excursions

Phase III

Process Qualification @ Scale

- Process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Ideal to “Lock in”
- Limited In Process Testing
- Trend Evaluation

Post Approval

Continued Process Verification

- Ongoing assurance during manufacturing that the process is controlled and the outcome predictable.

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Process Validation

Controlled process to assure consistent drug quality

Ideal to “Lock in”

- MCB/media
- Final DP formulation
- Unit Operations

Phase I/II Pre-optimized

Process Design

- Manufacturing process is defined during this stage and is based on knowledge acquired through development and scale-up activities

Cell Line Expression
CHO→ Multiple Expression Technologies
Start PD work on Pool

Media: Defined Animal Free - > No hydrolysates
Perform Enough Process Development to..

- Understand bioreactor set-points (pH, DO, Temp, RPM) and ranges
- Understand product quality during harvest
- Downstream to have NMT 3 chromatography steps.
- NLT 3 days of hold for at least 2 in process DSP steps
- Use catalogue raw materials that are scalable

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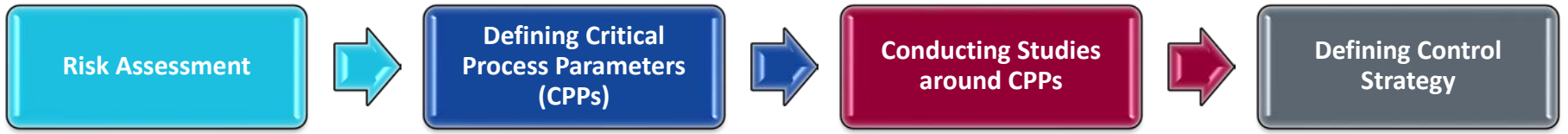
Late Stage Tasks

Late Stage Process Definition

Defining Control Strategies Based on Process Characterization Studies



Upstream

- Cell Culture Expansion Criteria
  - ✓ Densities
  - ✓ Cutback
  - ✓ Viability
- Bioreactor Controls
  - ✓ Temperature
  - ✓ DO set point
  - ✓ pH
  - ✓ Feeds Timing
  - ✓ Harvest Criteria
  - ✓ Growth trending
  - ✓ Product Quality

Downstream

- Load Density
- Column Collection Criteria
- Load Conditioning limits
- Impurity Removal
- Column Lifetime
- Viral Clearance Studies
- Wash Characterization
  - ✓ Salt content
  - ✓ pH
- Temperature
- Flow Rate
- UF/DF

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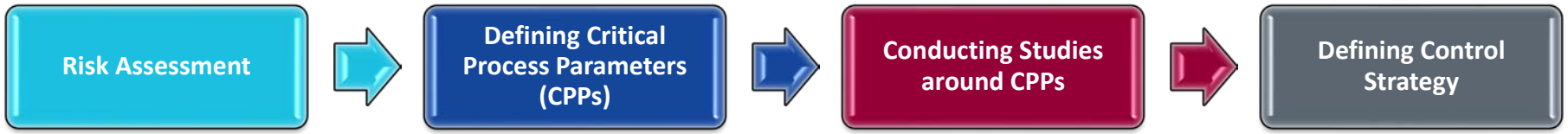
Late Stage Process Definition

Defining Control Strategies Based on Process Characterization Studies



Upstream

- Cell Culture Expansion Criteria
  - ✓ Densities
  - ✓ Cutback
  - ✓ Viability
- Bioreactor Controls
  - ✓ Temperature
  - ✓ DO set point
  - ✓ pH
  - ✓ Feeds Timing
  - ✓ Harvest Criteria
  - ✓ Growth trending
  - ✓ Product Quality

Early Stage Lessons

- Avoid cutbacks too close to stationary phase
- Avoid any transition from one media to another during expansion
- Avoid spinner flasks, shake flasks and Waves only
- Avoid continuous feeds, use bolus only
- Ideal to have feeds based on time, not VCC
- Ideal to mimic temp shifts as they would occur at scale (meaning slower)
- Ideal to determine if any product impact from transient excursions
- No hydrolysates in feeds or basal media

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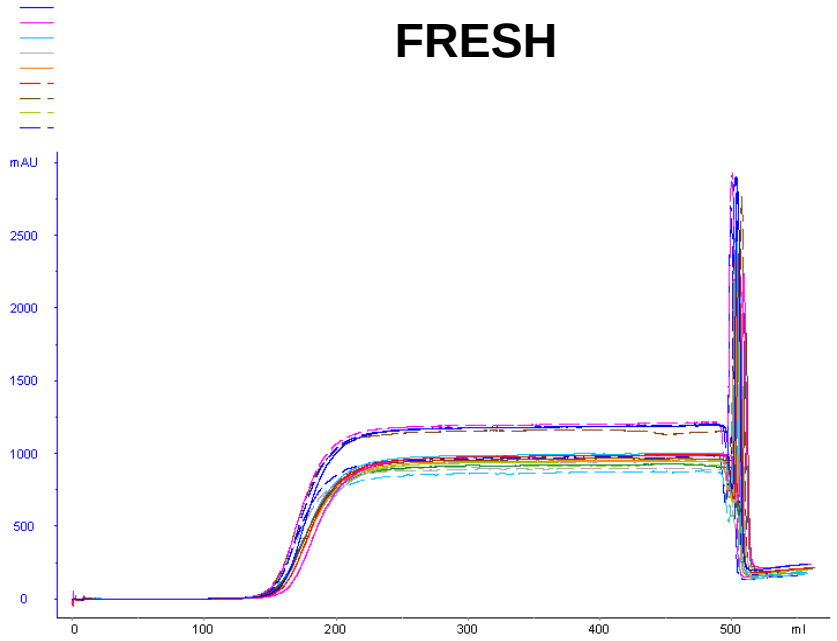
Late Stage Process Definition

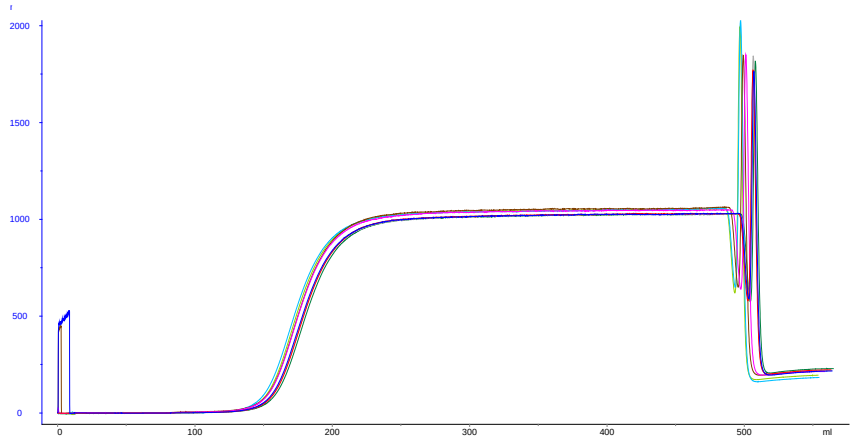
Defining Control Strategies Based on Process Characterization Studies

Virus Validation

FRESH



USED



	Fresh	
Sample	Replicate #1	Replicate #2
Load	8.07	8.09
Flow Through	<3.02	<3.01
LRV	>5.05	>5.07

	Used (57 Cycles)	
Sample	Replicate #1	Replicate #2
Load	8.24	7.85
Flow Through	< 2.74	< 2.74
LRV	≥ 5.50	≥ 5.11

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Early Stage Development that Facilitates Late Stage Virus Validation

1. Qualified a small scale model in PD
2. No change in the resin manufacturer
3. Comparable product residence time
4. In Phase I VV, operate the column at highest product load to mimic worst case
5. Qualified a small scale model in PD
6. No change in the load conditions → Cytotoxic / interference is critical
7. Early lifetime studies gave confidence of multi-use performance (vendor data too)
8. No change in the post use CIP → good to show no carryover after virus spiking when column was stripped and cleaned with MFG CIP.

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More Late Stage Tasks

Upstream

- Filtration Media Studies
- Media Hold Time
- Upstream (Media and Feed) Mixing
- EOPC
- Inoculum Expansion Robustness

Downstream

- Downstream Mixing (S2L)
- Downstream Mixing (L2L)
- Extractable/Leachable
- Column Carryover
- In-process Hold Times
- Column Short Term Hold
- Column Long Term Hold
- Membrane Sanitization
- Membrane Re-use
- Resin Lifetime
- Impurity Clearance
- Viral Validation
- Buffer Hold Times
- Homogeneity

Supporting

- Container Integrity Study
- Freezing
- Shipping
- Stability
- Freeze-thaw
- Equipment Calibration or Validation
- Raw Material Evaluation

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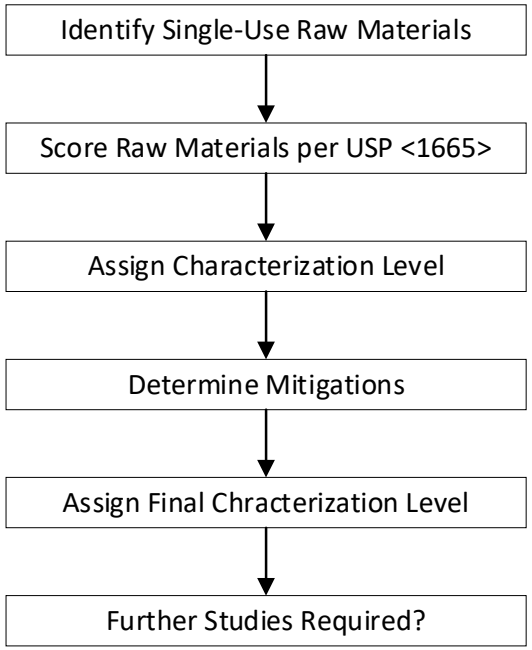
Late Stage Process Characterization
Extractable and Leachable Studies

APPROACH



SCORING

Risk Dimension	Scoring
Duration	Score 1: < 24 hours Score 2: 1 – 7 days Score 3: > 7 days
Temperature	Score 1: < 0°C Score 2: 2-25°C Score 3: > 30°C
Fluid Chemical Composition	Score 1: Aqueous (< 5% Organic); pH ≥ 3 and ≤ 9 Score 2: Somewhat Organic (5% - 40% Organic) Score 3: Highly Organic (> 40% Organic); pH < 3 or > 9
Disposable Material of Construction	Score 1: Inert Score 2: Intermediate Score 3: Reactive

EXAMPLE

Dimensional Scores	Example Dimensional Score	Characterization Level
Three or four dimensions score level 3	3333 or 3332 or 3331	Level C
Two dimensions score Level 3	3322 3321 3311	Level C Level B or C* Level A or B**
One dimension scores Level 3	3222 or 3221 3211 3111	Level B Level A or B** Level A
No dimension scores Level 3	2222 2221 or 2211 or 2111 or 1111	Level B Level A

→ Obtaining information on polymeric resins is time consuming– requires communication with multiple vendors
→ “ABC” characterization level from USP<665> and <1665>

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USE CONSISTENT FILM THROUGHOUT PROCESS!

Process Qualification

Resin Lifetime/Impurity Clearance - To ensure consistent impurity removal and product quality is achieved across the resin lifetime

At early stage, qualify a small scale model, perform some limited lifetime studies

Also, ideal to understand HETP/As values as it relates to performed

CRITICAL FOR PRE-PACKED COLUMNS

Small-Scale

Feedstock from GMP
Or applicable scale-down model

Test for Impurities, Recovery, Product Quality Attributes throughout lifetime

MFG-Scale

Feedstock from GMP

Test for Impurities, Recovery, Product Quality at defined intervals and at the end of lifetime

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Process Qualification

In Process Hold - To ensure the biochemical nature of the product does not change over a defined hold time and microbial ingress does not occur during the hold

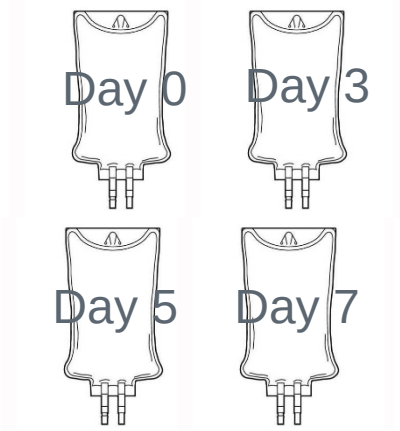
At early stage, perform holds in same film as late stage

Small-Scale

Feedstock from GMP

Test for product-related impurities

Store in small bags



MFG-Scale

Feedstock from GMP

Test for product-related impurities and BB/LAL

Day 0 **Day 3**

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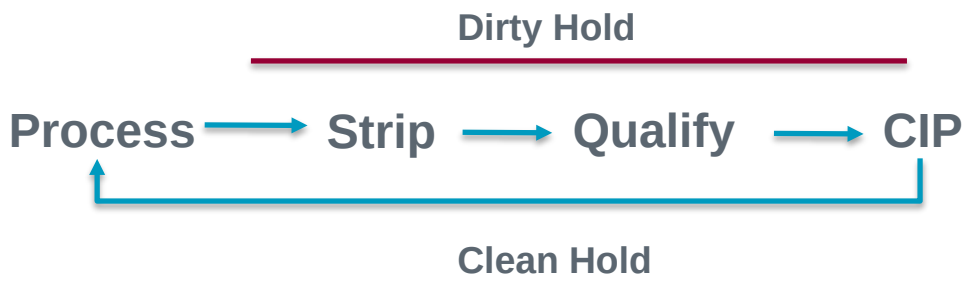
Process Qualification

Column Hold (Clean and Dirty) - To ensure columns are maintained in a state of microbial control



Early stage:
Strip and clean per vendors recommendations

MFG-Scale

Feedstock and CIP from a GMP lot.

Test for LAL and Bioburden at the end of each hold

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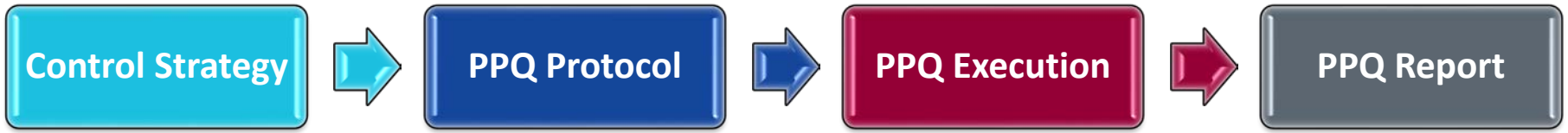
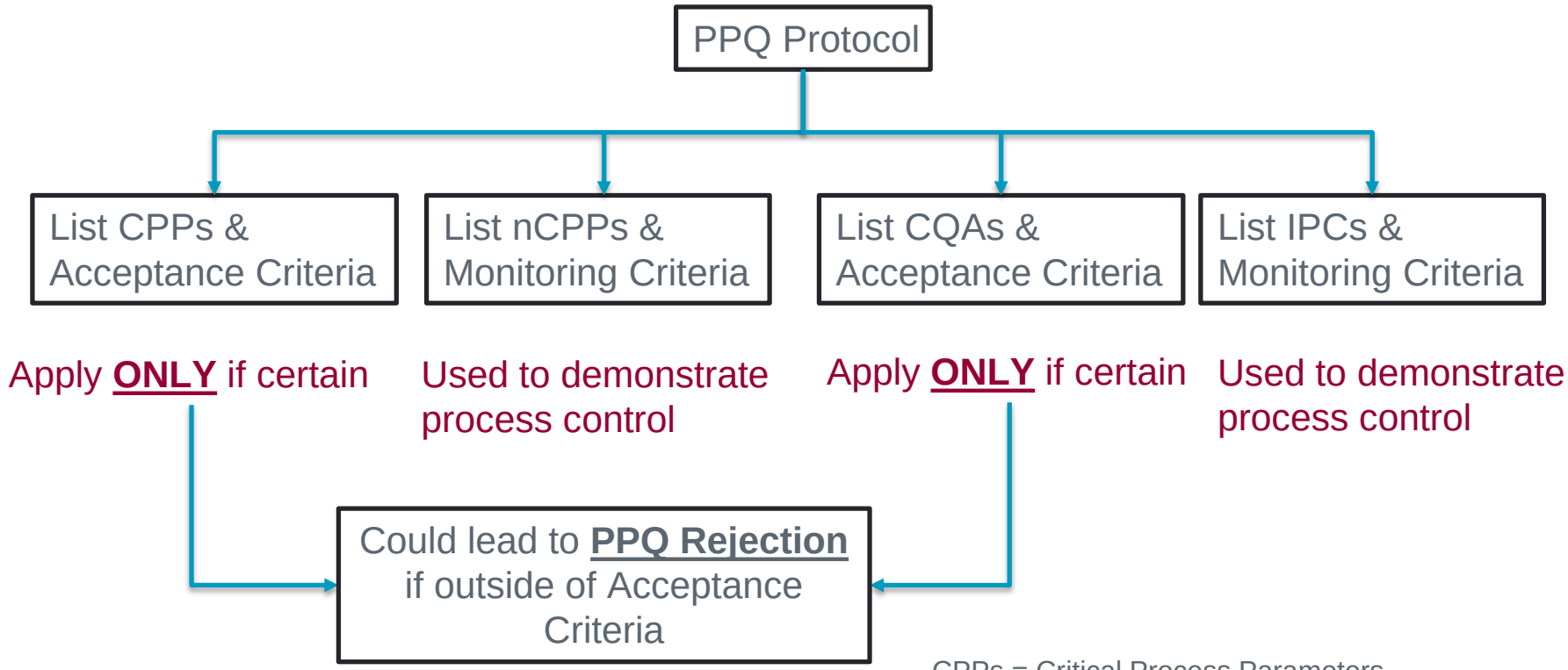
Process Performance Qualification @ Scale

Defining Parameters and Quality Attributes



Early stage:
Do not assume a parameter is critical. Special care to be taken to set Acceptance criteria (easier to tighten in late stage than vice versa)



CPPs = Critical Process Parameters
nCPPs = Non-Critical Process Parameters
CQAs = Critical Quality Attributes
IPCs = In-Process Controls
PPQ = Process Performance Qualification

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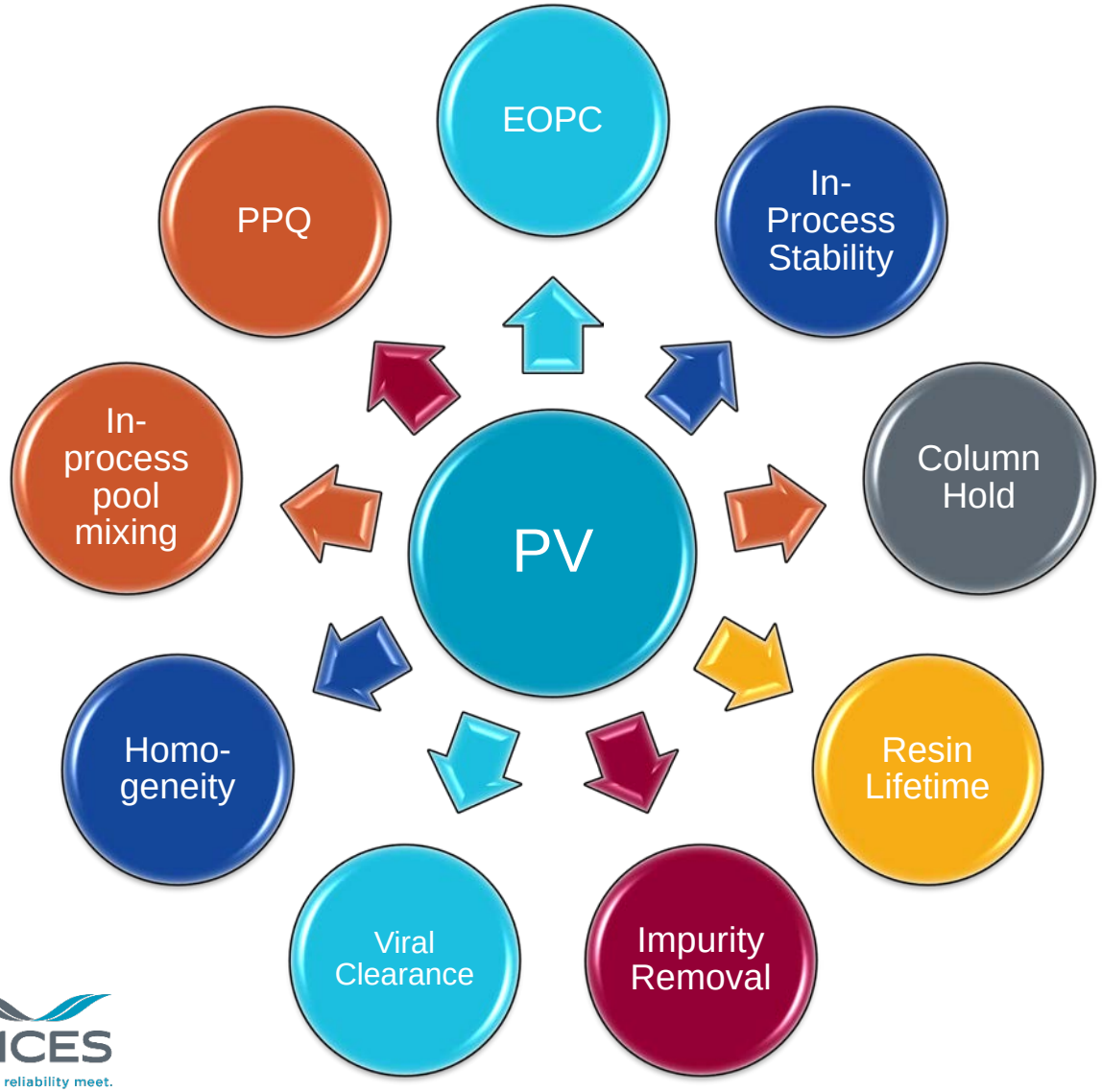
Late Stage Process Validation

Collecting Significant amount of Data from Various Studies



Challenges

- Samples for supporting studies can account for >> 100s of additional samples/batch
- Requires coordination amongst different groups to pull, transfer, test, document the samples

In the early stage:
Prioritize process simplification
Understand sample stability
Understand assay performance with the sample matrix

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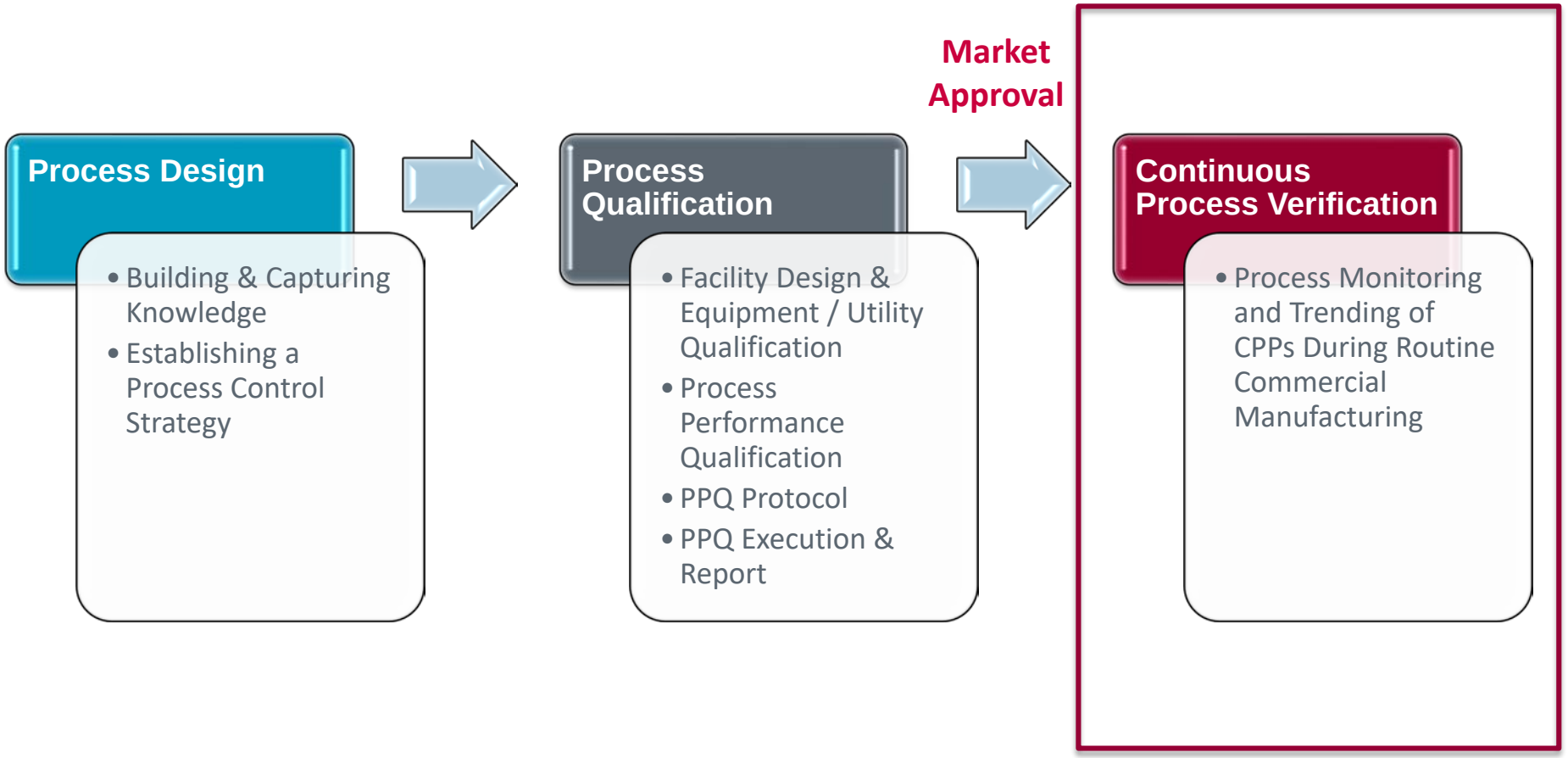
Process Monitoring (Post PQ)

Avid's Process Validation Approach



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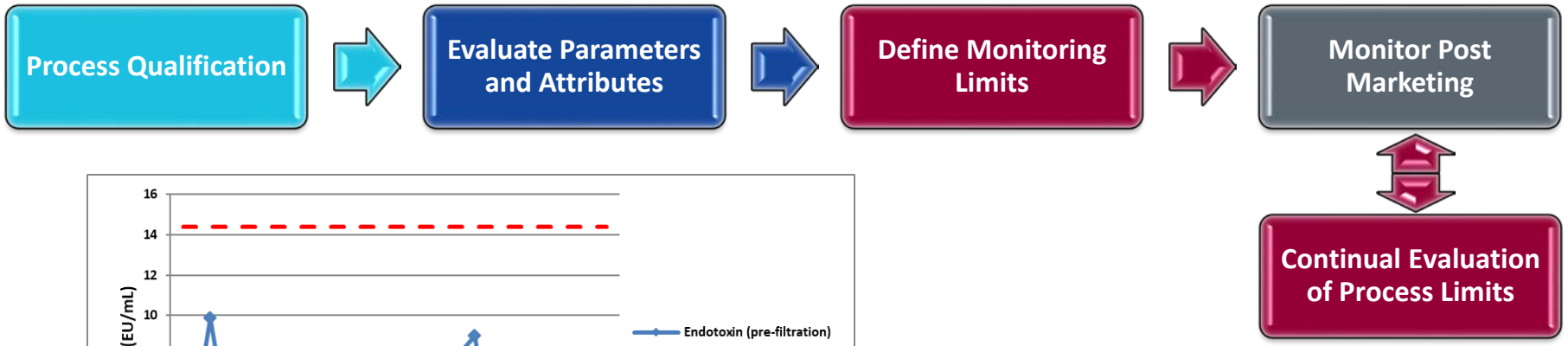
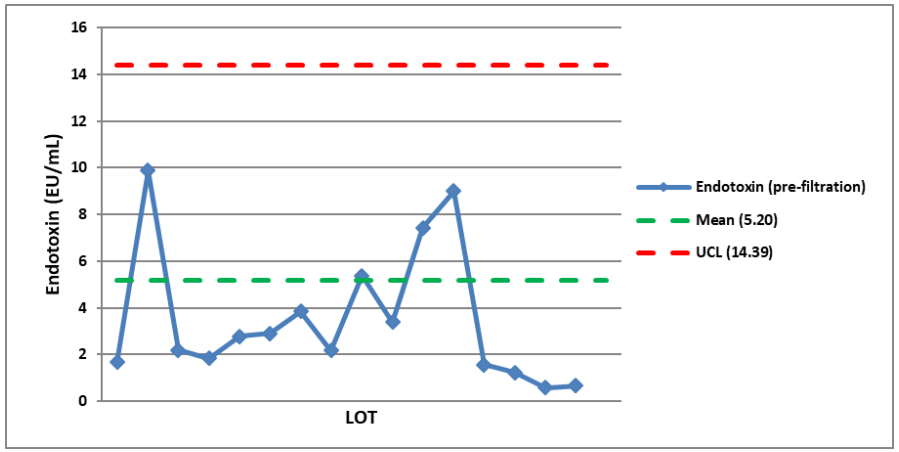
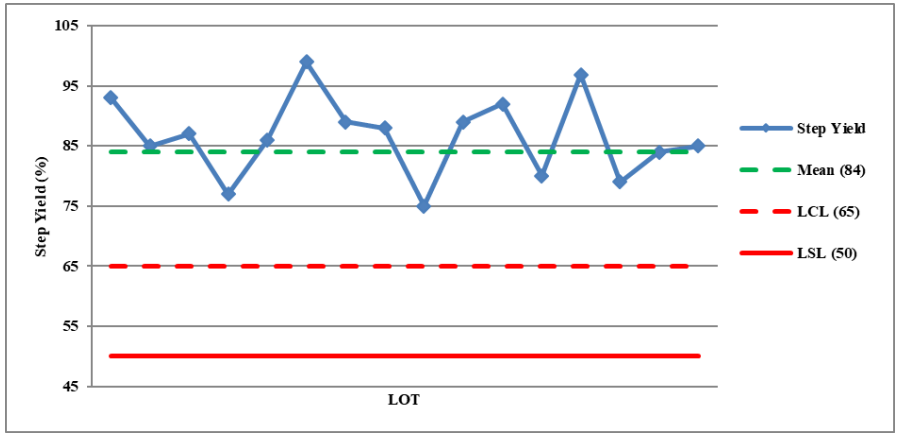
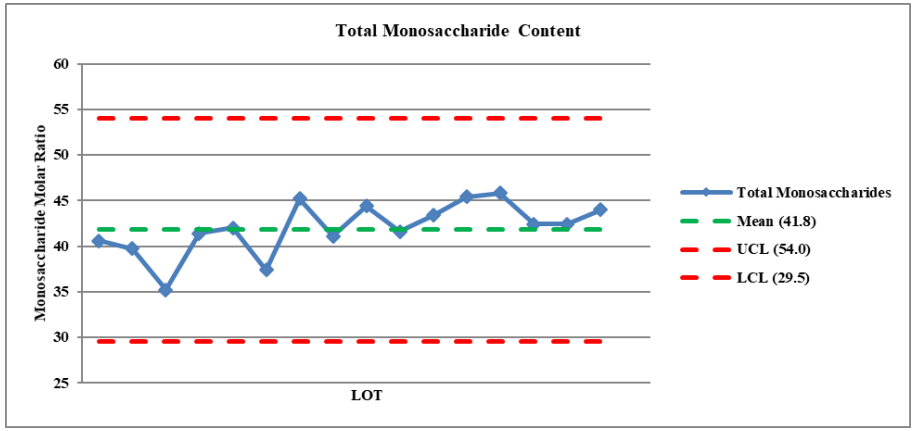
Continuous Process Verification

Ensures commercial process is in a state of control









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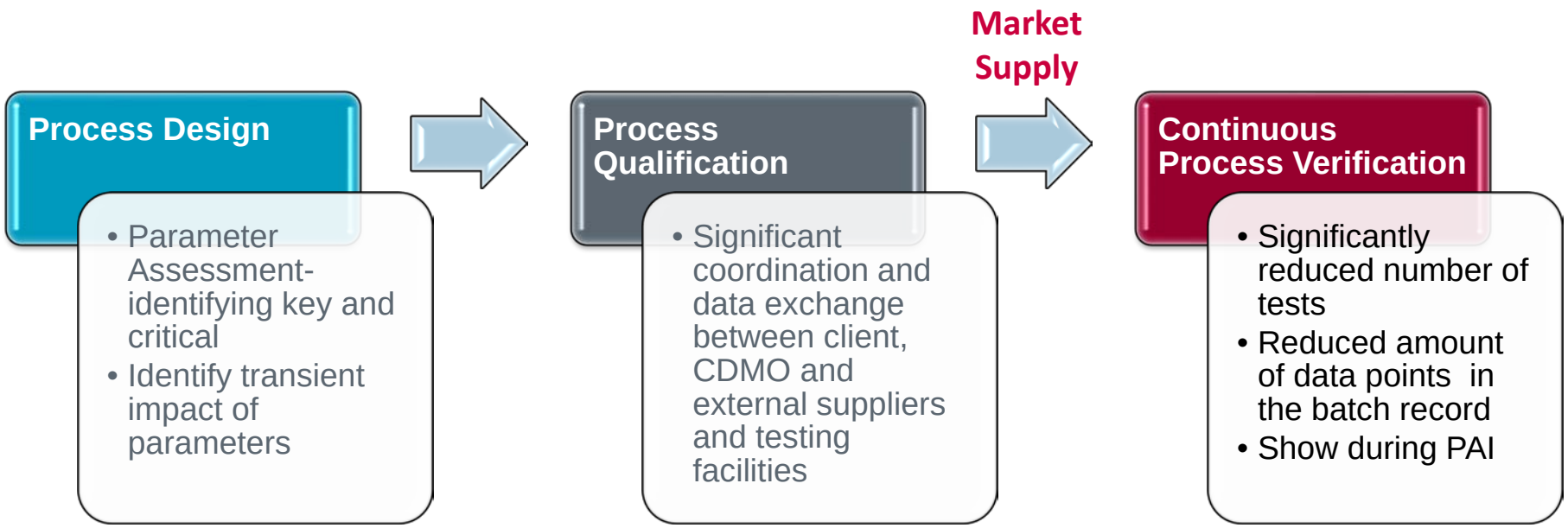
Key Factors



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Early Process Development Considerations

1. Choosing a CLD Technology
   - Pool ~ final clone to allow early start to PD
   - Defined media and feeds already selected → reduces media and reactor parameter screening
   - High commercial titers are now common for early phase → no need to change for late stage
2. CHO cells are now routinely reaching >50M cells/mL
   - Harvest is now an extremely critical step to understand
3. Execute the process in a small scale model (preferably Pilot) before large scale
   - DO Control (some cell lines require up to 15-20LPM of O_2 @ the 2KL scale!)
   - CO_2 stripping
   - Shear in the reactor and harvest
4. USP and DSP goal is to have as small # of unit operations as possible
   - 5:1 Turndown reactors
   - Expansion criteria
   - Three chromatography steps
   - Create a process where the product flow from one unit operation is the load for the next
5. Finalize drug product formulation (admittedly hard to do)
   - Can leverage into process knowledge for in process formulations
6. Select the vendors with strong GMP history
   - Avoid “beta testing”, newer untested technologies

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Thank You

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