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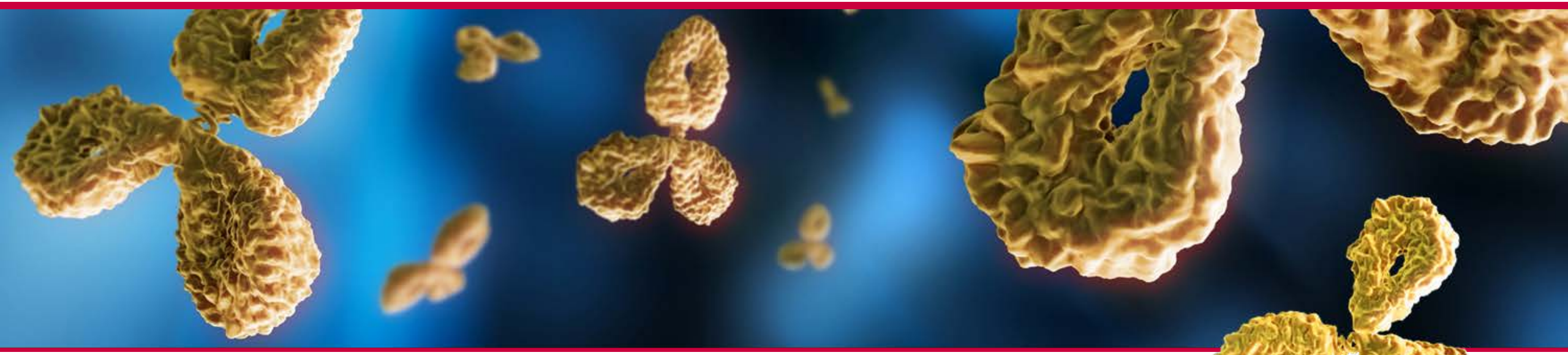

Road to Commercialization – a CDMO Perspective

Richard Richieri
Chief Operations Officer
Avid Bioservices, Inc.

Tuesday, September 10th, 2019

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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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

- 42,000 ft² open space
- Facility Design with twice the capacity as Myford 1

6 x 2,000L

4 x 200L

Actual configuration TBD

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End-to End Solutions

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CDMOs are an Important Partner to the Biopharmaceutical Industries

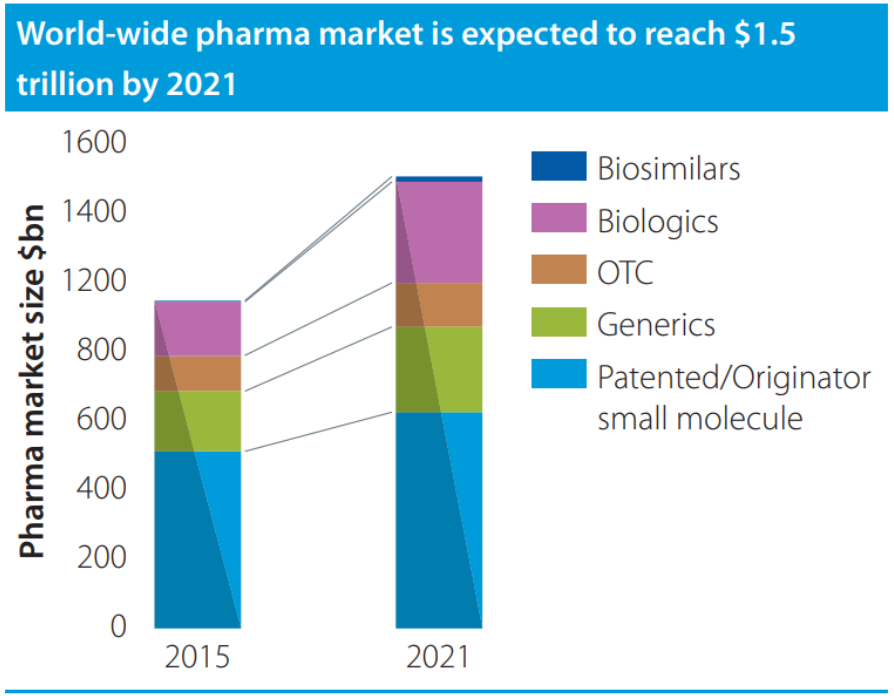

Figure 1 *Global pharmaceutical market 2015-2021*

- 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
  - ➢ 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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Road to Commercialization

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."

Process Design	Process Qualification @ Scale	Continued Process Verification
• Manufacturing process is defined during this stage and is based on knowledge acquired through development and scale-up activities	• Process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.	• Ongoing assurance during manufacturing that the process is controlled and the outcome predictable.

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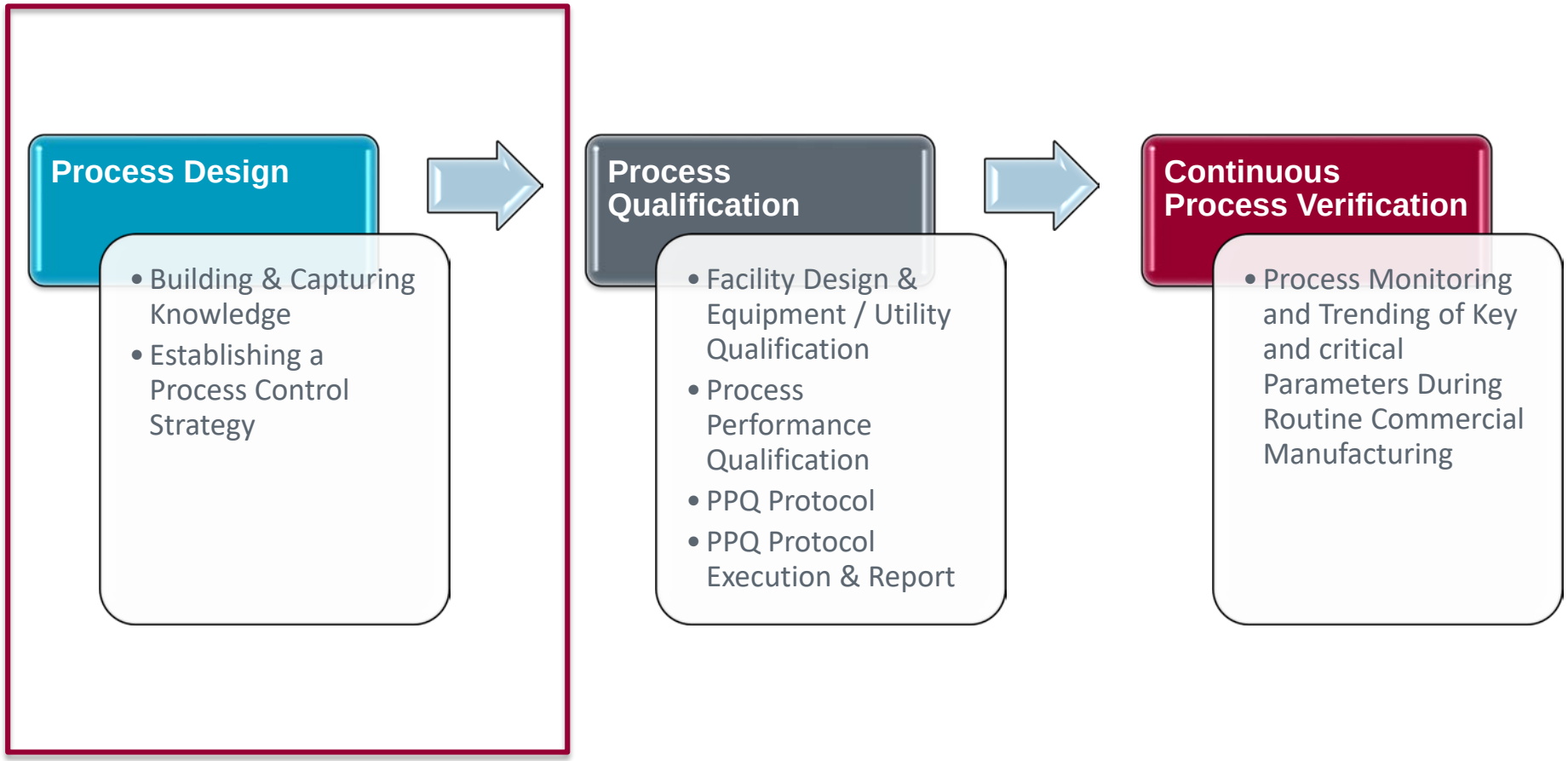
Avid's Process Validation Approach



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Process Design

Process Design

Defining Control Strategies Based on Process Characterization Studies

Risk Assessment → **Defining Critical Process Parameters (CPPs)** → **Conducting Studies around CPPs** → **Defining Control Strategy**

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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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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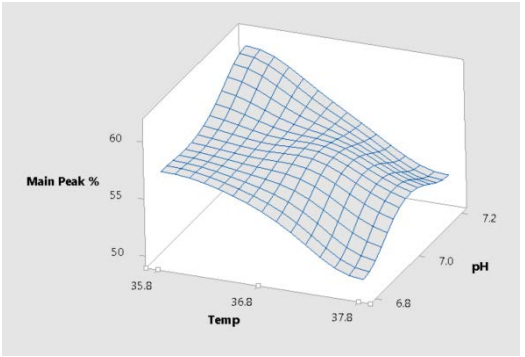
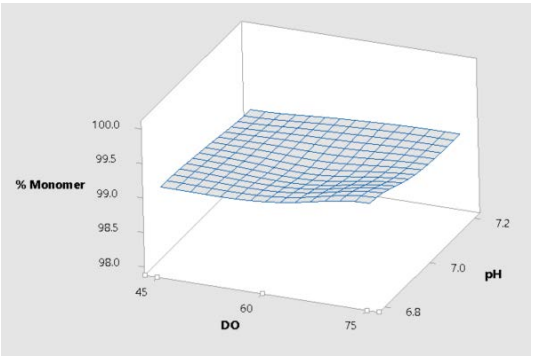
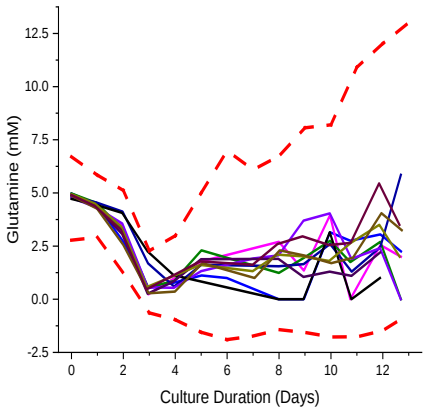
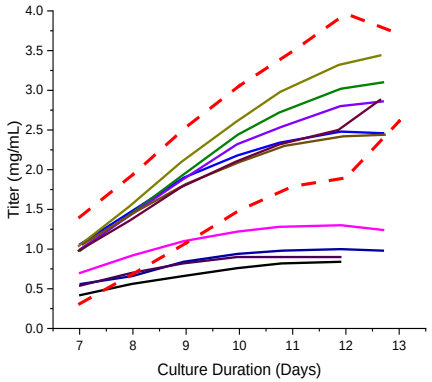
Process Characterization DOE
Defining the Process Design Space









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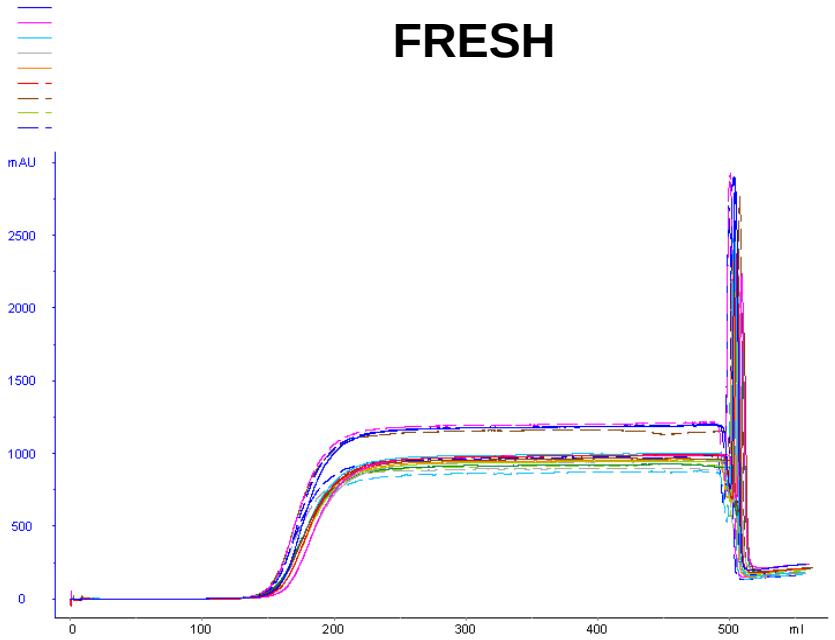
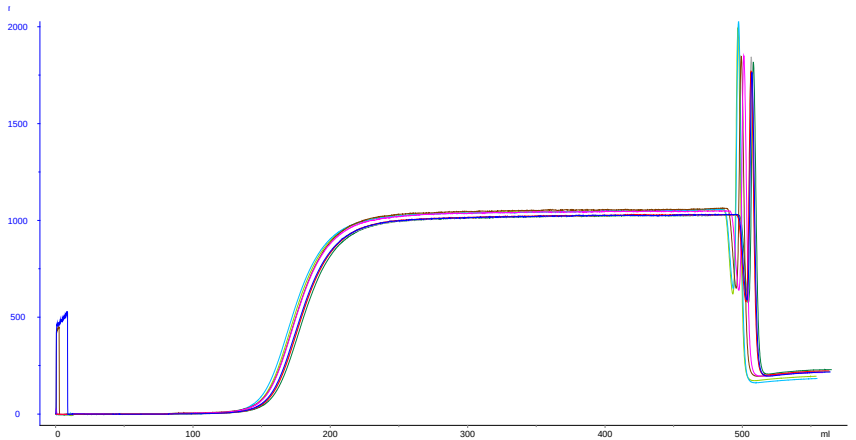
Process Characterization
Virus Validation

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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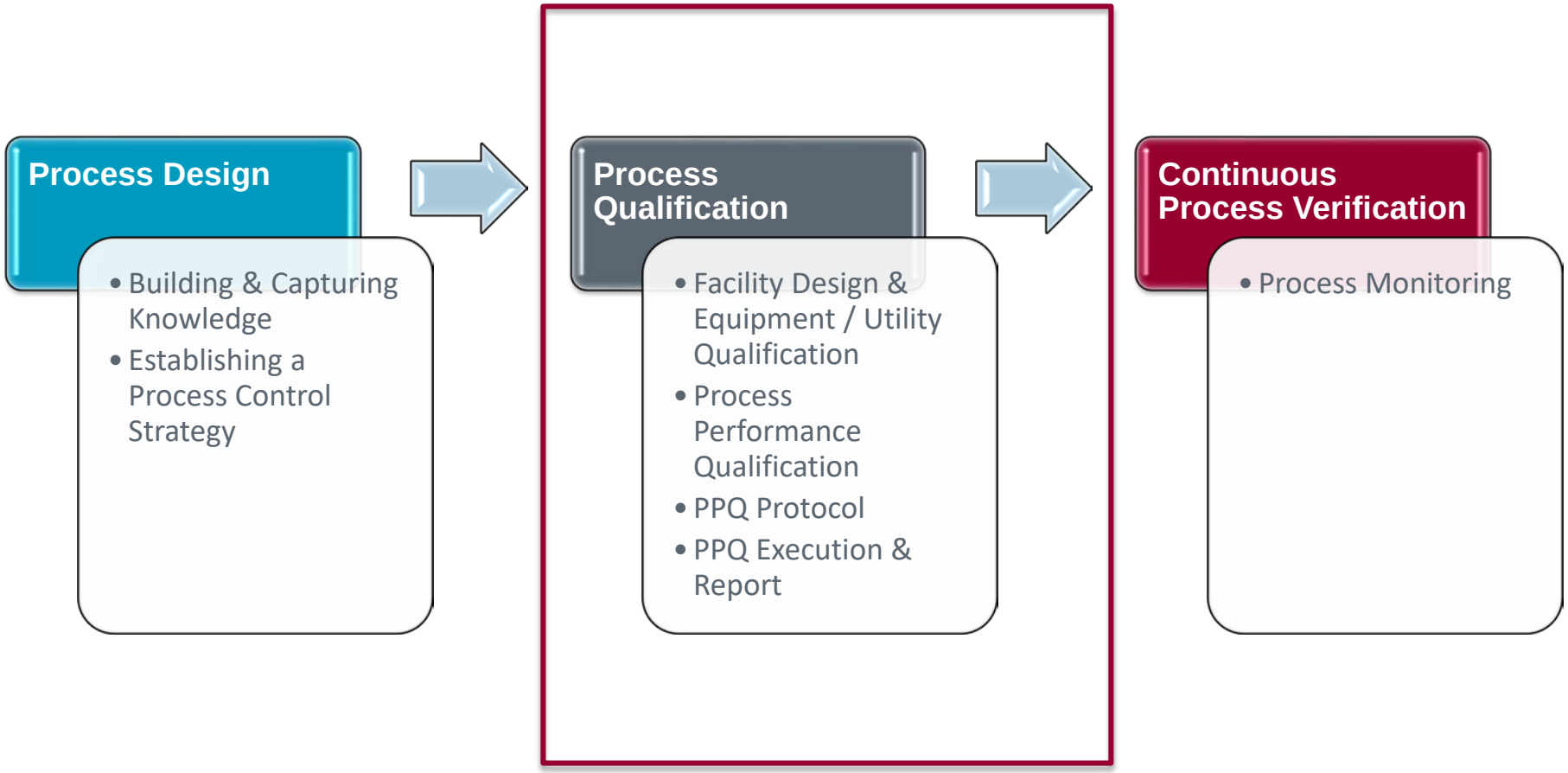
Process Characterization
Virus Validation

1. Operate the column at highest product load to mimic worst case
2. Cytotoxic / interference is critical
3. Must meet acceptable yield as defined by DSP DOE, also chromatogram shape
4. Used vs Fresh: have to use exact MFG method to clean (Phase III specific)
5. LRV from Used and New resins should be comparable
6. Good to show no carryover after virus spiking when column was stripped and cleaned with MFG CIP.
7. Virus titer stocks are getting more concentrated, may be possible to perform a subset of the steps to achieve the desired LRV

Process Qualification

Avid's Process Validation Approach



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Process Qualifications Require the Completion of Numerous Studies

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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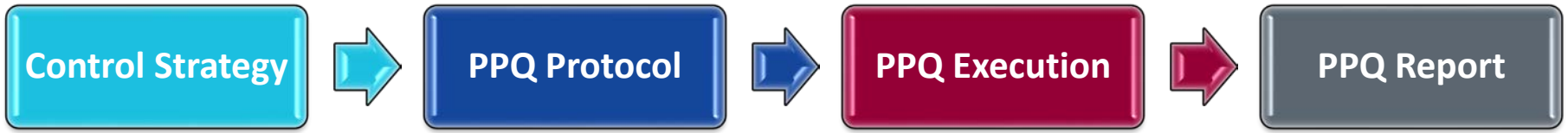
Process Performance Qualification @ Scale

Defining Parameters and Quality Attributes



PPQ Protocol

List CPPs & Acceptance Criteria	List nCPPs & Monitoring Criteria	List CQAs & Acceptance Criteria	List IPCs & Monitoring Criteria
Apply **ONLY** if certain	Used to demonstrate process control	Apply **ONLY** if certain	Used to demonstrate process control

Could lead to **PPQ Rejection** if outside of Acceptance Criteria

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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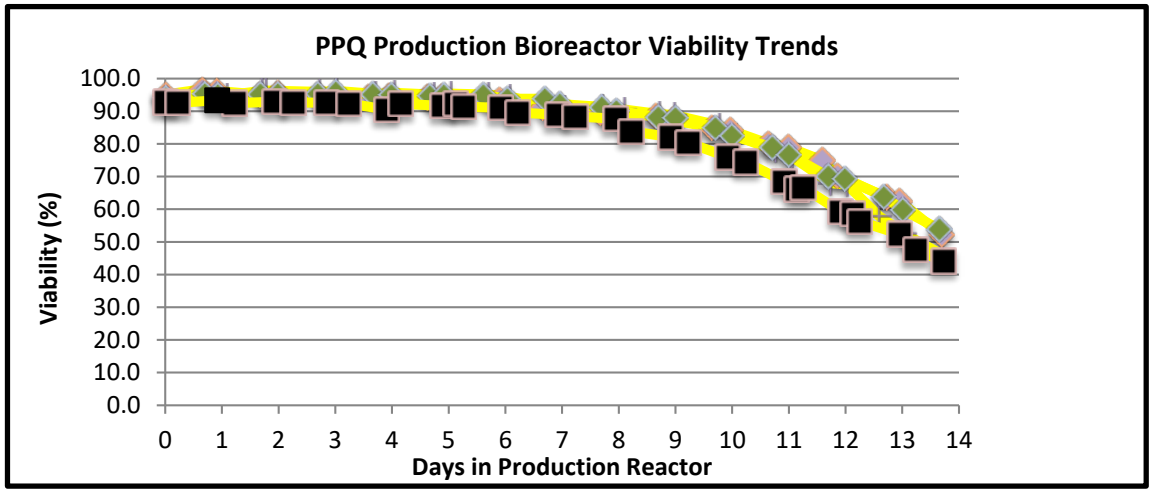
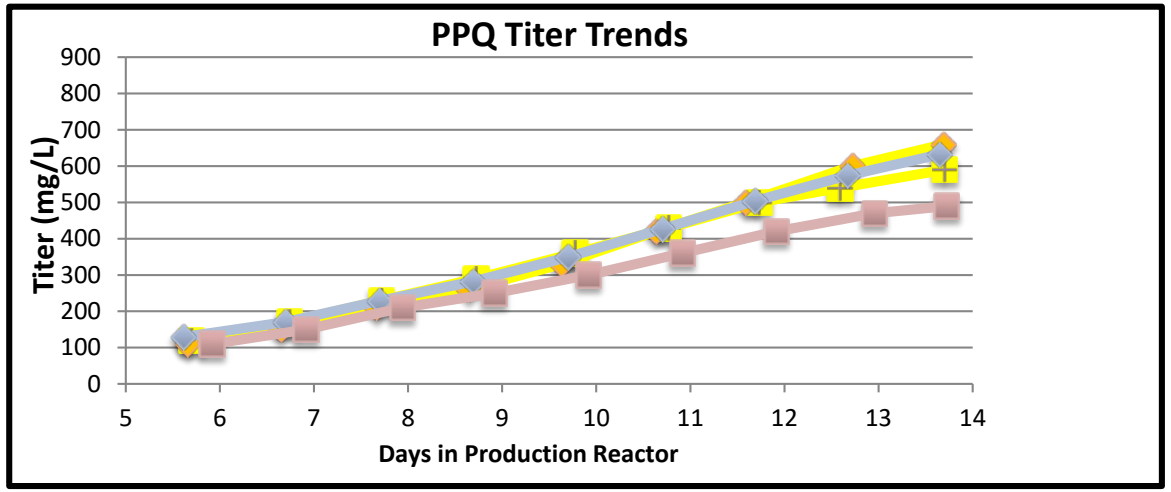
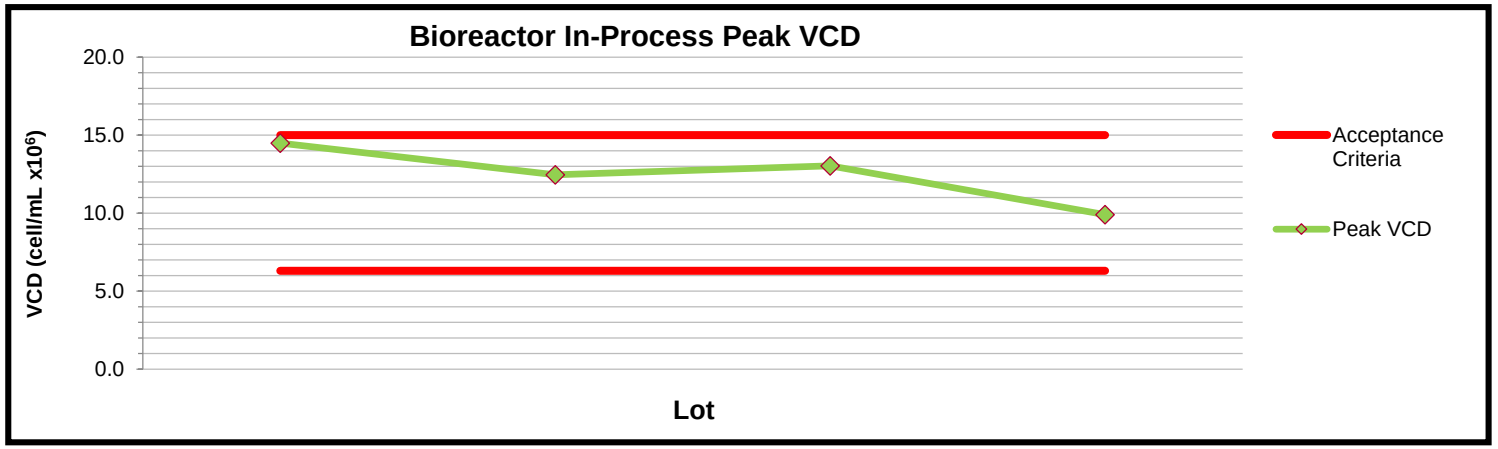
Process Qualification
Completed Batches Exhibit Process Robustness and Meet Acceptance Criteria







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Process Qualification
Extractable and Leachable Studies

Operation	Component Description	Dimensional Score	Risk Dimension
MabSelect SuRe Purification (AKTA Ready)	AKTA pH probe	3211	Level A
	Stapure Element tubing, 12 mm	3211	Level A
	Size 73 Tubing	3211	Level A
	100L Palletank Bag with Bottom Port and 45000cm2 filter, sterile	2211	Level A
	Tubing Assembly w/sample port	3211	Level A
	100L Mixtainer Bag	2111	Level A
	AKTA Ready High Flow Kit	3211	Level A
	0.2 µm PES Opticap XL 10 with size 73 tubing on outlet, sterilized	2111	Level A
	Size 73 Tubing	2111	Level A

The risk increases closer to BDS; Level B and C require additional testing

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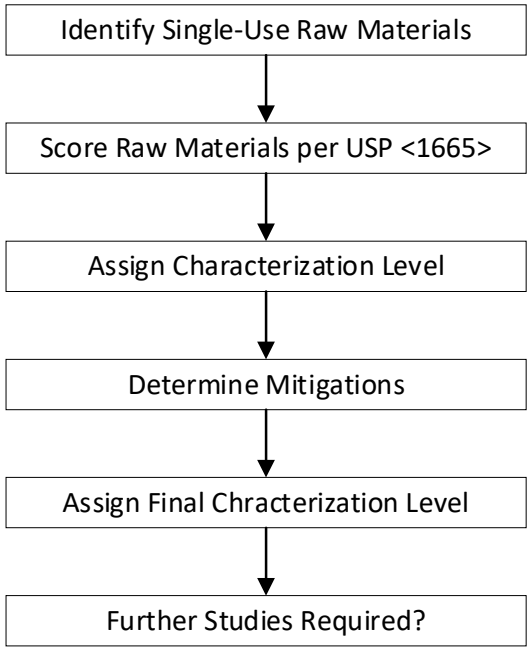
Process Characterization
Extractable and Leachable Studies

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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Process Characterization
At Scale Blank Run Carryover Study for Purification Columns

- A Full-Scale run performed after a Manufacturing run to demonstrate no carryover
- Under protocol, with acceptable criteria for product concertation and process related impurities (HCP, DNA)
- Same buffers as MFG
- Loads are without protein but use same buffer
- Load volumes are calculated from MFG Batch records
- Elution volumes are calculate from MFG batch records.
- **Collection start volume and collected weight for each step:**
  - For each operation, collection start volume were based on the volume from the start of the elution step to the start of eluate collection.
- Eluate collection was stopped when the collection weight reached the same amount as GMP run

Typically 3 log reduction from production values generally used

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Process Qualification

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

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

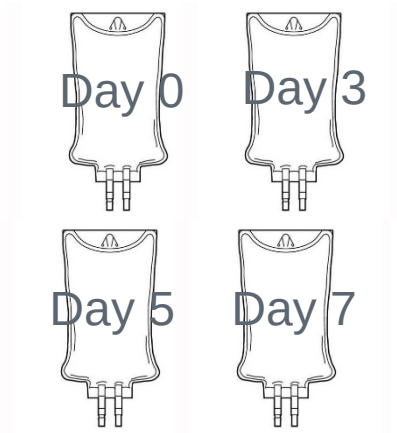
In Process Hold - To ensure the biochemical nature of the product does not change over a defined hold time and microbial ingress does not occur during the hold

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

Dirty Hold

Process → Strip → Qualify → CIP

Clean Hold

MFG-Scale

Feedstock and CIP from a GMP lot.

Test for LAL and Bioburden at the end of each hold

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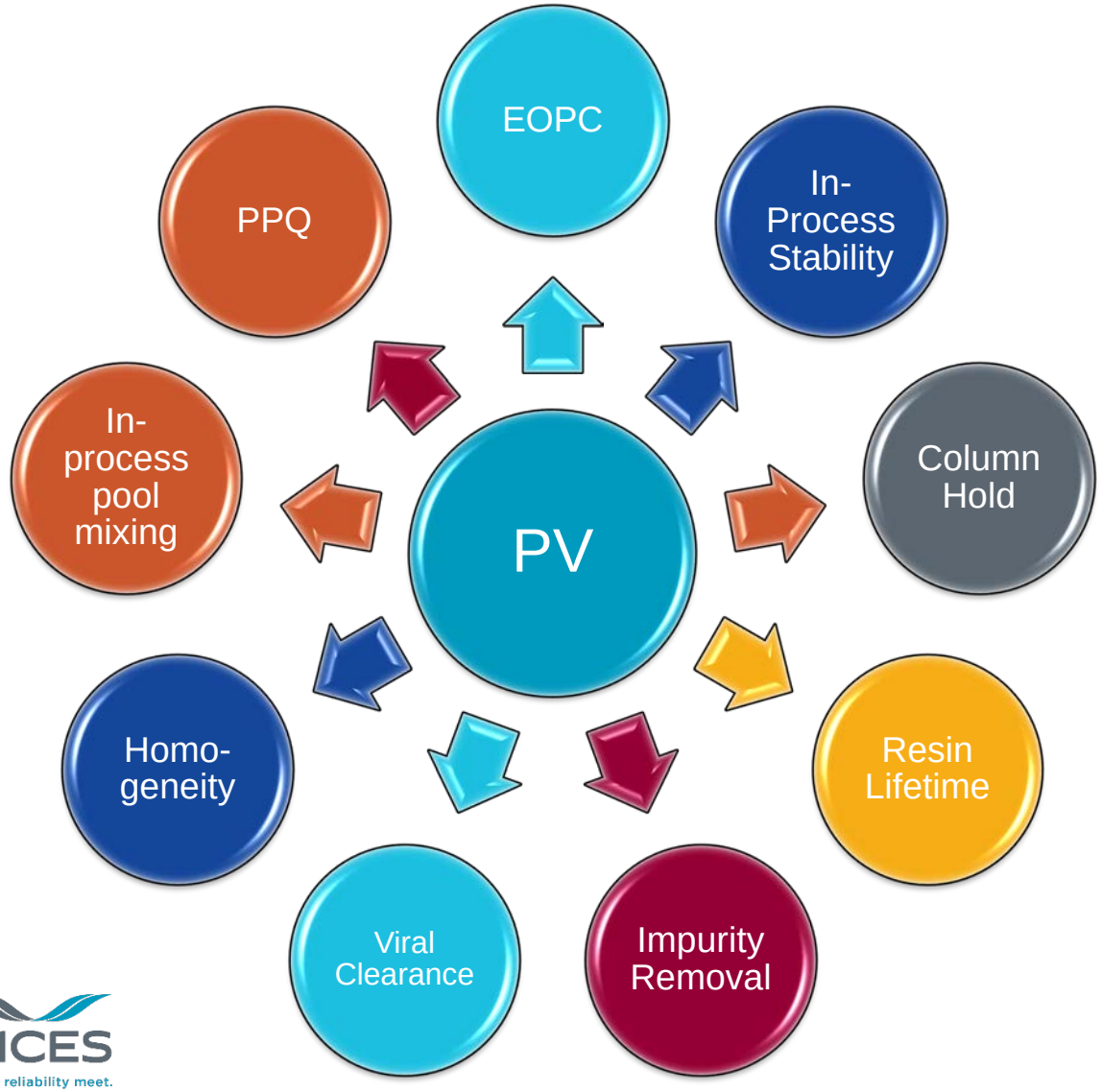
Process Validation

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

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Process Monitoring (Post PQ)

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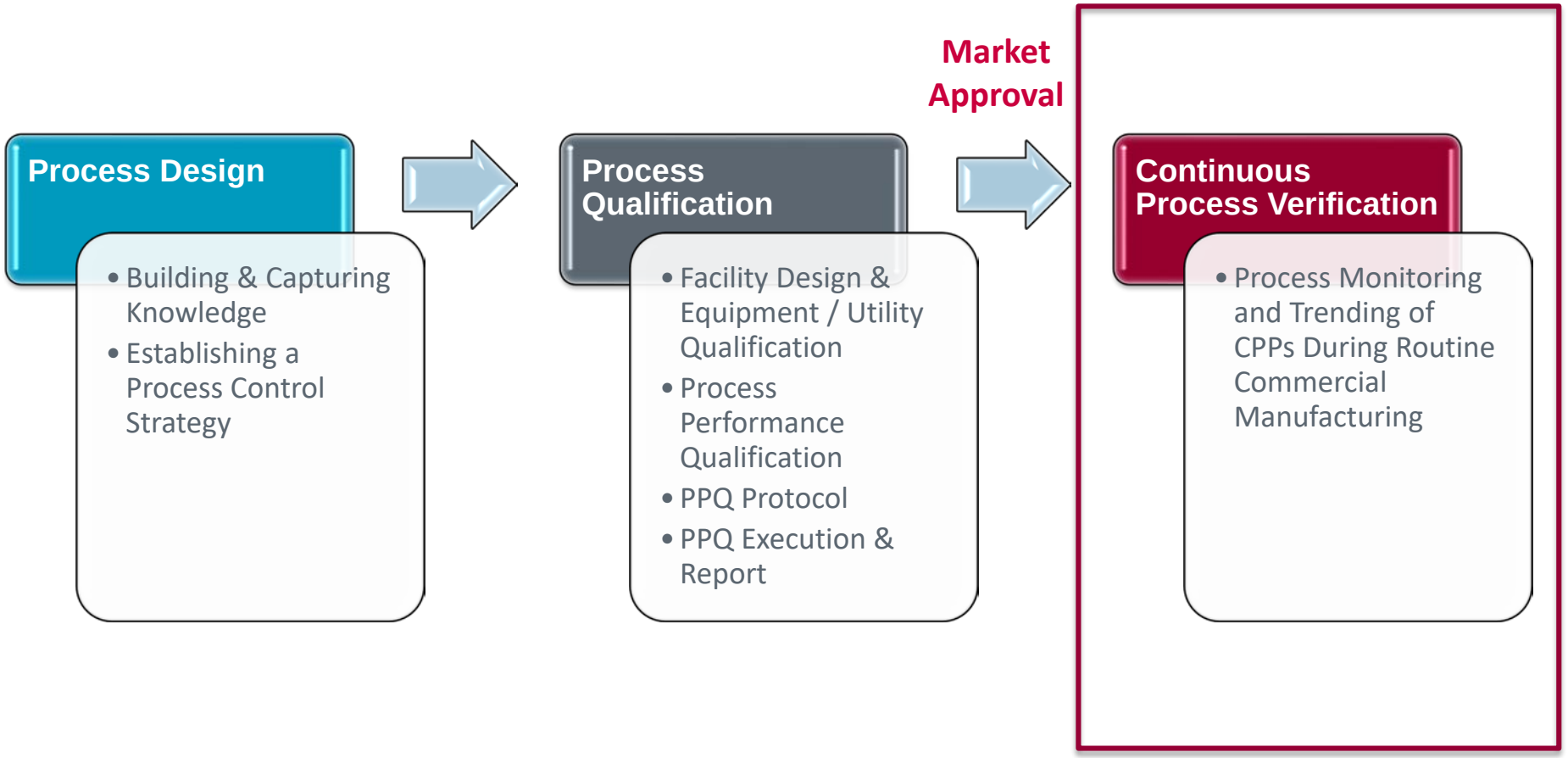

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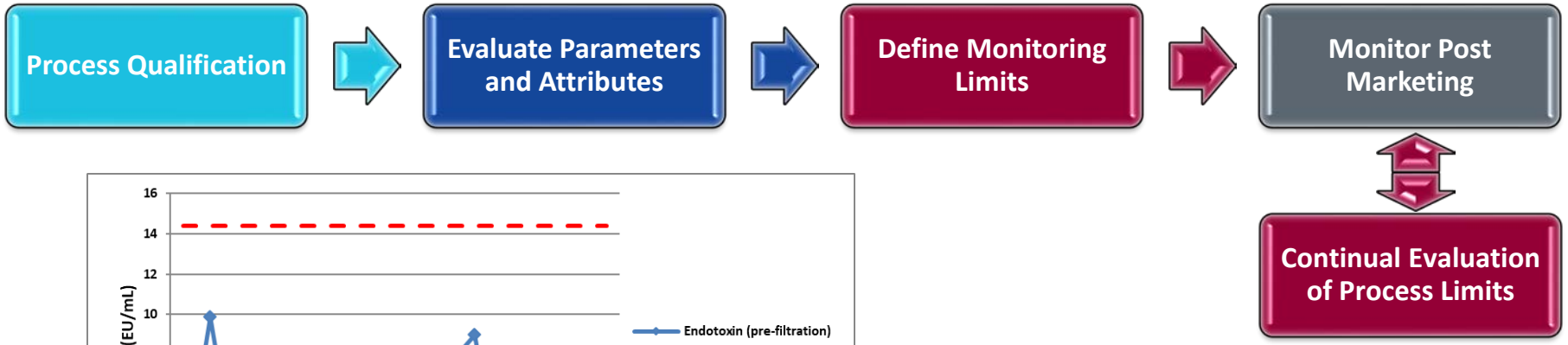
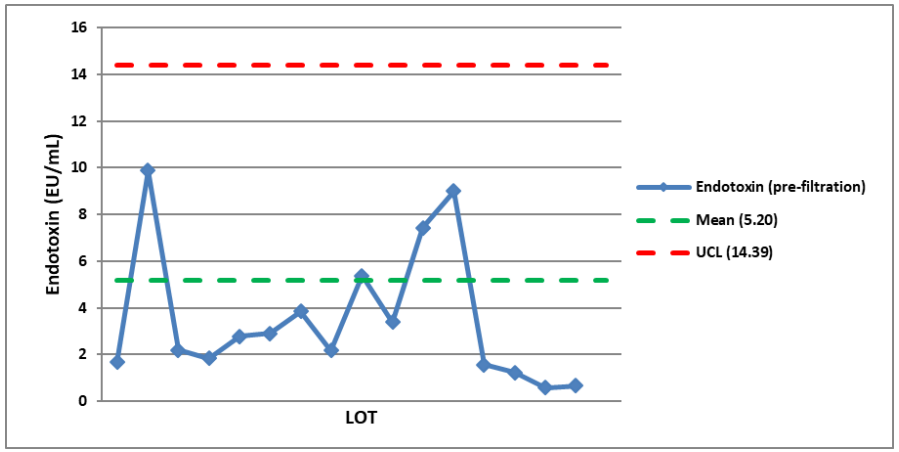
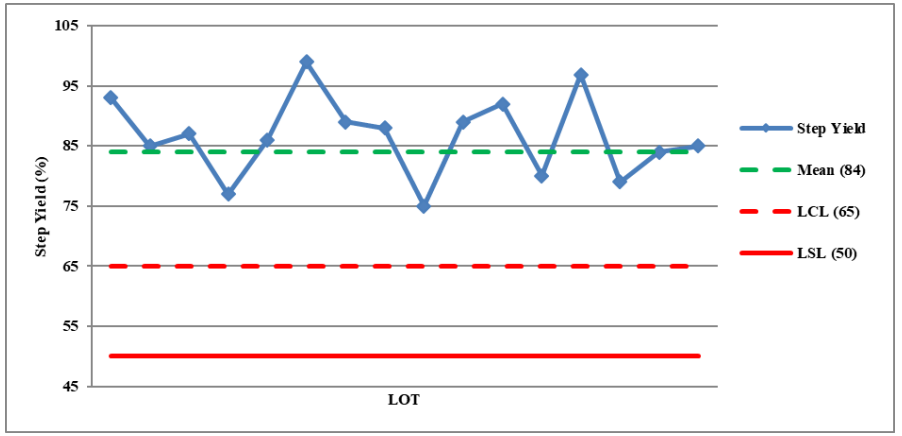
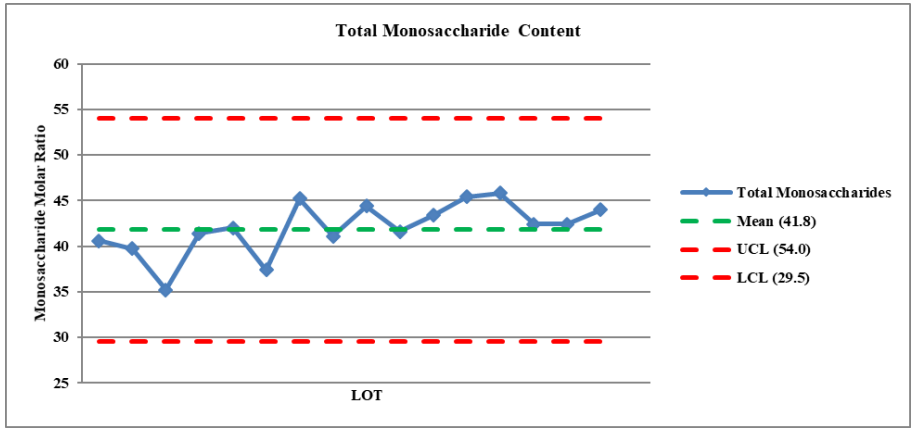
Continuous Process Verification

Ensures commercial process is in a state of control









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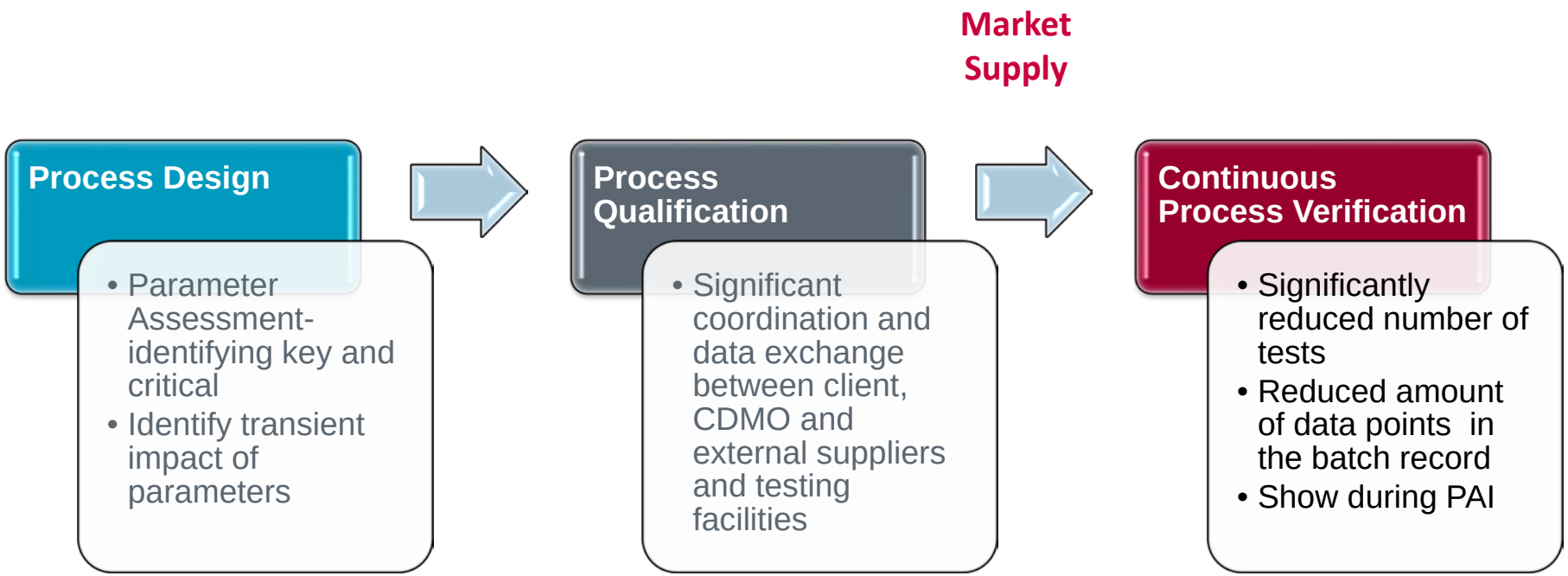
Key Factors



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Thank You

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