Avid Case Study – Taking Your Molecule Through Process Validation

AVID BIOSERVICES

IMPROVING PATIENT LIVES

by consistently delivering high-quality biopharmaceutical products

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Project Manager

Interphex 2019

Wednesday, April 3, 2019

Presentation Objective

To share Avid's experiences in planning, executing, and completing process validation campaigns

William Leonardi

Will be presenting the planning cycle of Process Validation Campaign

Avid Bioservices Overview

- Avid Capabilities and Track Record Supporting Multiple Process Validation Campaigns

Process Validation Planning

- Project Management Involvement in Process Validation Life Cycles

David Briggs

Will be presenting the execution cycle of Process Validation Campaign

Process Validation Execution

- Avid Approach in Executing Process Validation Campaign

Summary

- Key factors to ensure the execution of Process Validation

CDMOs are an Important Partner to the Biopharmaceutical Industries

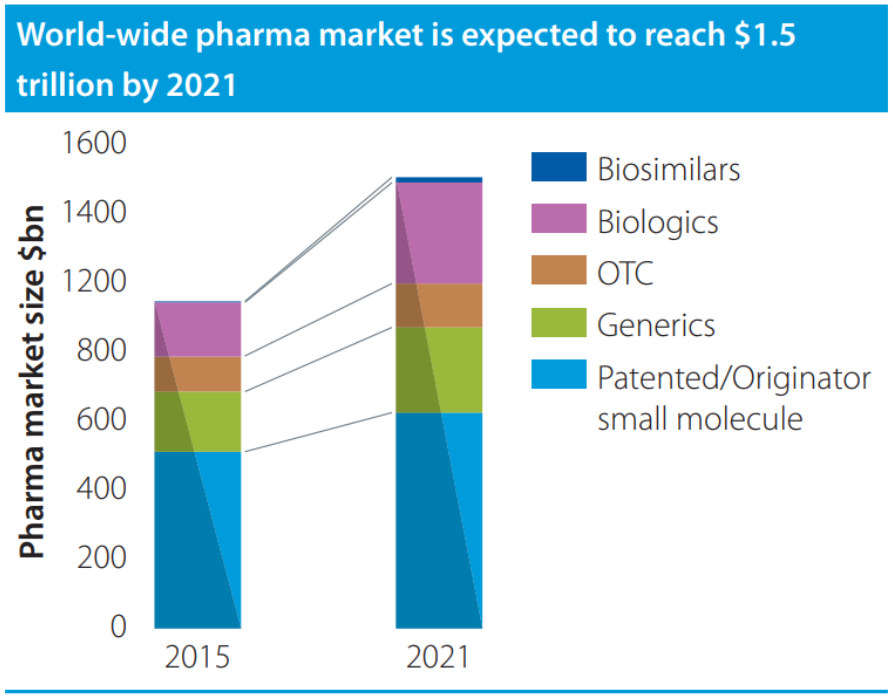


Figure 1 *Global pharmaceutical market 2015-2021*

- Biologics and Biosimilar show a faster paced growth than among other sectors (22.2% market share in 2021 vs 16.6% in 2015)
- 220 New Drugs are expected to be introduced in 2021 (biologics products lead the growth) – Demand for biologics manufacturing will increase
- The introduction of new biologic products to the market will require biopharma companies to build inventory prior to launch – Partnering with CDMO to secure the supply
- Externalizing manufacturing of biologic products to CDMO is highly desirable to reduce time to market and operational expense - pharma and biotech companies can focus on its core capabilities and strengths

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

Source:
- *Review of Outsourced Manufacturing. Results Healthcare Report. 2017*
- *Outlook of Global Medicines through 2021. QuintilesIMS*

AVID BIOSERVICES

Avid Bioservices Overview

Established Track Record as a Clinical & Commercial Biologics CDMO

26+ Years of experience developing in-house product & technology

26+ Years of biologics manufacturing experience

14+ Years of successful inspection history

14+ Years of cGMP commercial manufacturing

11+ Years of with single-use technology, multiple platforms

9 Successful process validation campaigns

6 Successful pre-approval inspections

FDA U.S. FOOD & DRUG ADMINISTRATION

ANVISA Agência Nacional de Vigilância Sanitária

Paul-Ehrlich-Institut

Republic of Turkey Ministry of Health

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

Australian Government Department of Health

Health Canada

AVID BIOSERVICES

State of The Art cGMP Manufacturing Facilities

Commercial manufacturing since 2005

Fully disposable manufacturing process

Future Expansion

Facility Overview

Franklin Facility

- 12,000 ft^2 facility
- cGMP manufacturing since 1993
- Inspected by multiple regulatory agencies

Myford 1 Facility

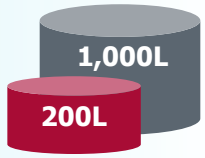
- 42,000 ft^2 facility
- Commissioned in 2016
- Integrated QC labs for in-process samples, final release, & environmental monitoring

Myford 2 Expansion

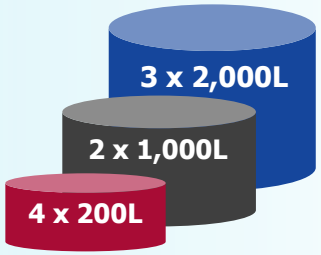
- 42,000 ft^2 open space
- Facility Design with twice the capacity as Myford 1

Capacity

Stainless Steel



Single-use



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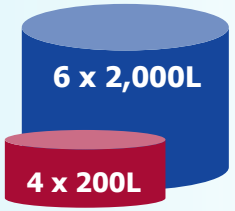


Single-use

Actual configuration TBD

Process Validation Campaign Planning

Process Validation

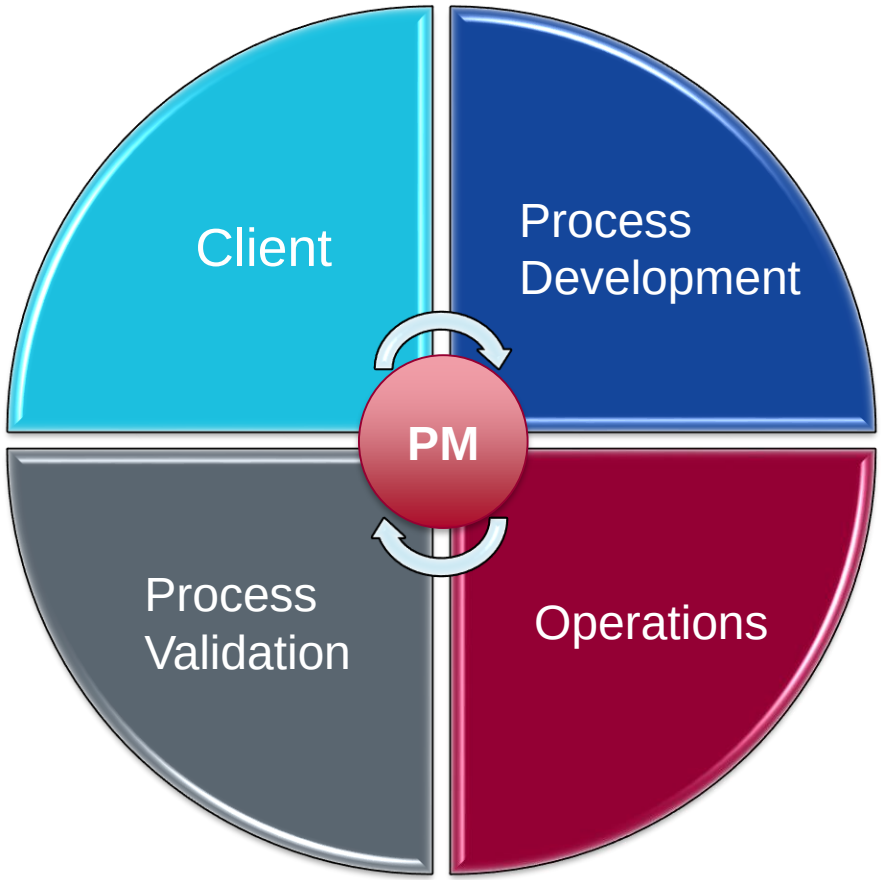
Controlled process to assure consistent drug quality

According to the FDA's 2011 Process Validation (PV) guidance, "For purposes of this 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	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.

Project Management Hands On Involvement Throughout Process Validation Life Cycle

Avid Project Manager (PM) works focused on managing the overall life cycle of Process Validation by 1) Planning and Coordinating multiple activities and 2) Providing real time information's and Outstanding customer services to multiple stake holders

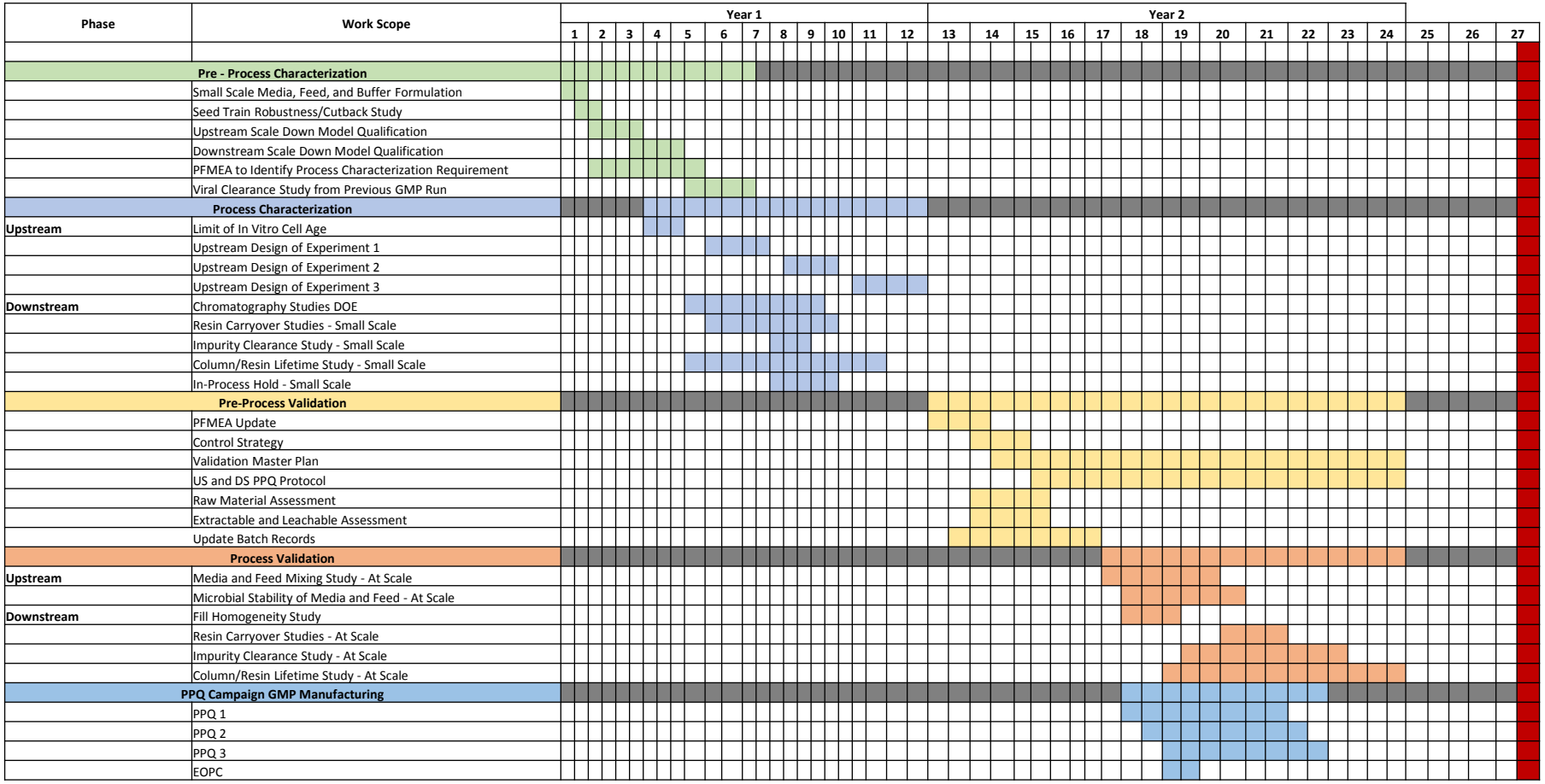


Process Validation Planning Life Cycle

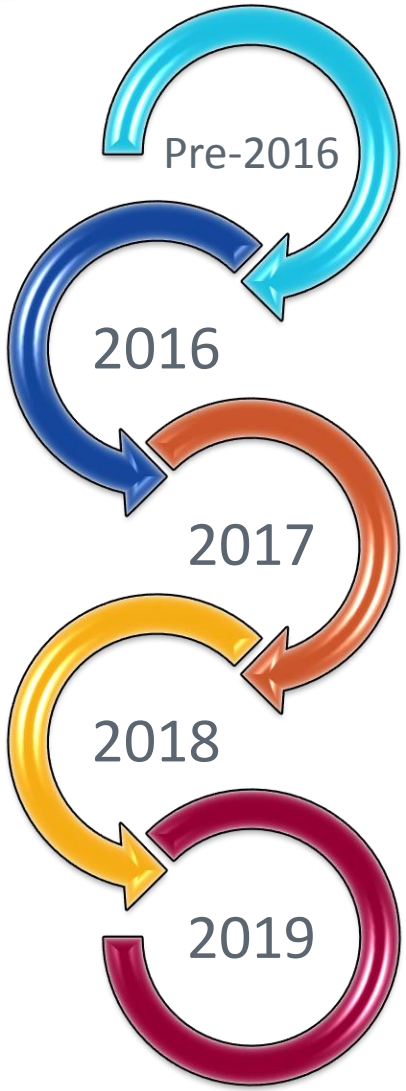
Initiation	Planning	Monitoring and Control	Closure
1. Estimate BLA submission time 2. Determine study requirements 3. Determine process validation strategy	1. Timeline generation. 2. Identify and confirm responsible lead 3. Finalized Project Charter 4. Stakeholder approval	1. Periodical meeting (internal and external) 2. Identify corrective actions 3. Any additional project/studies needed 4. Change Order to update timeline	1. Complete and formally close related projects 2. Communicate project closure to stakeholders

Tailored Approach to Plan and Manage Overall Process Validation Life Cycle

- Avid Project Manager (PM) works closely with external and internal clients to ensure the Process Validation strategies are aligned with the client regulatory submission strategies
- Work breakdown structures will be managed by a dedicated Avid PM



Avid Has Experience Conducting 10 Process Validations



Successfully executed 3 Process Validations and 2 resulted in commercial products

Successfully executed 2 Process Validations

Successfully executed 2 Process Validations

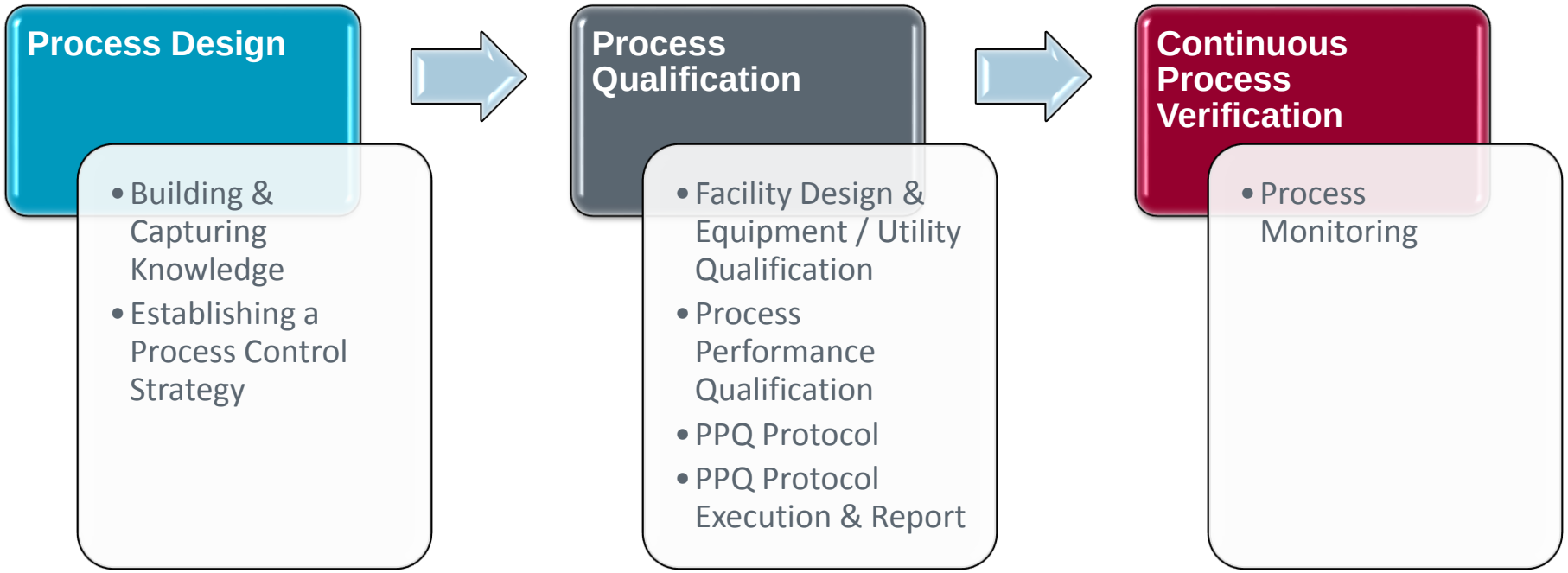
Successfully executed 1 Process Validation

Successfully executed 1 Process Validation

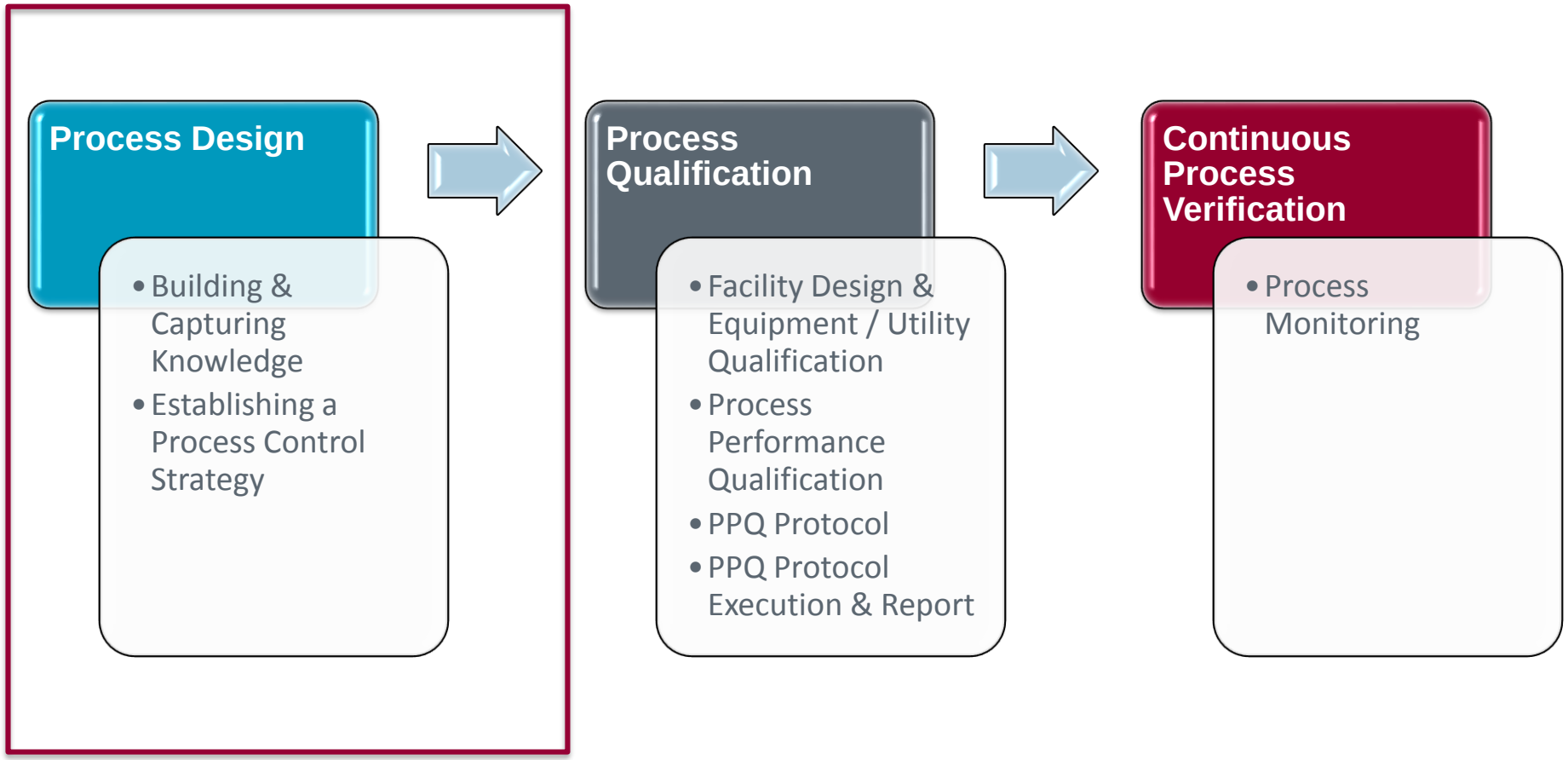
1 Process Validation is on-going

Avid Case Study

Avid's Process Validation Approach



Avid's Process Validation Approach



Process Design

Defining Control Strategies Based on Process Characterization Studies

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

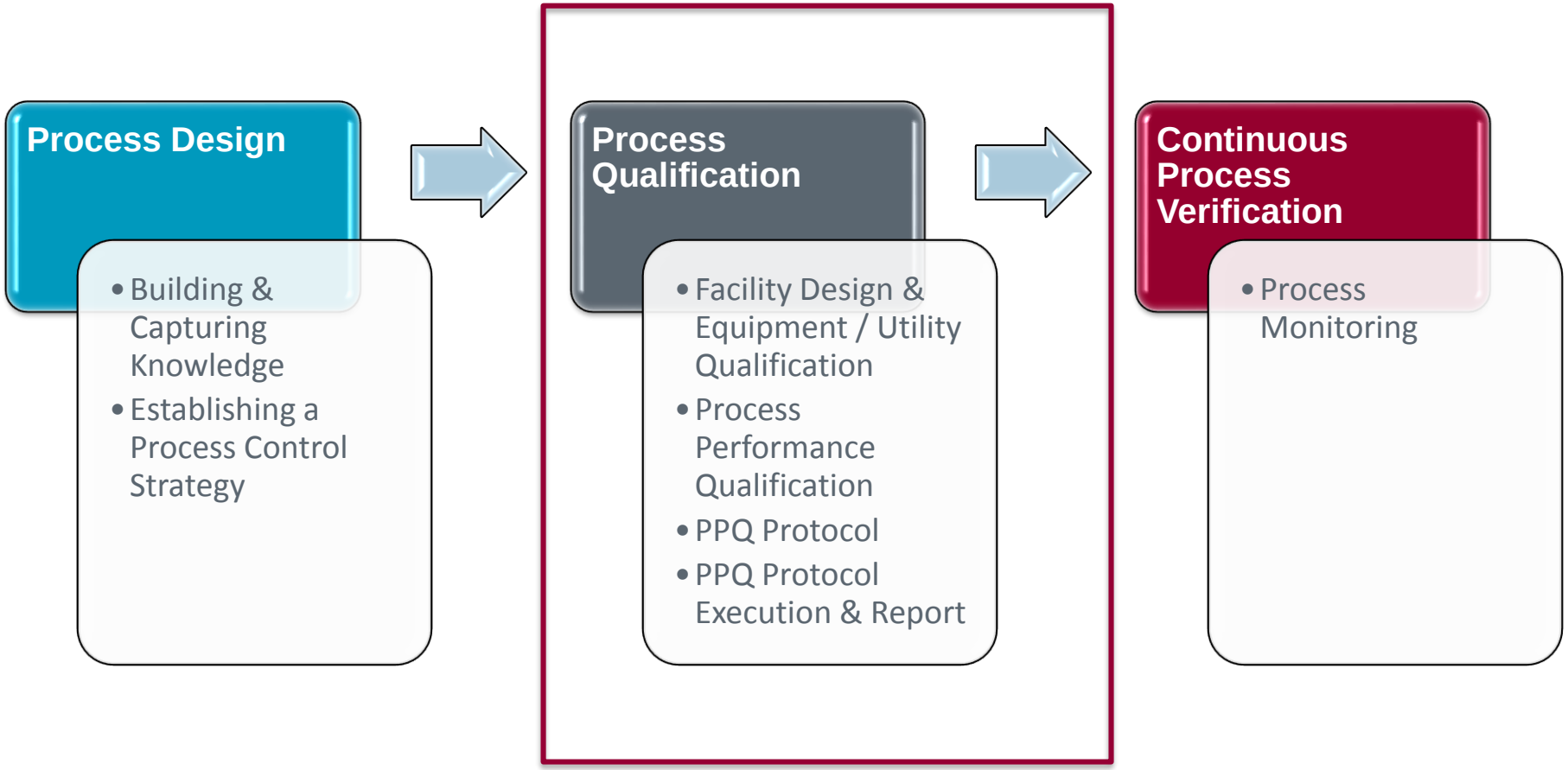
Upstream

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

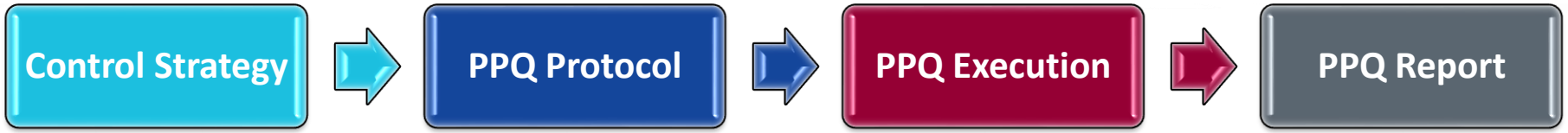
Downstream

- 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

Avid's Process Validation Approach



Process Qualification
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

Process Qualifications Require the Completion of Numerous Studies

Upstream

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

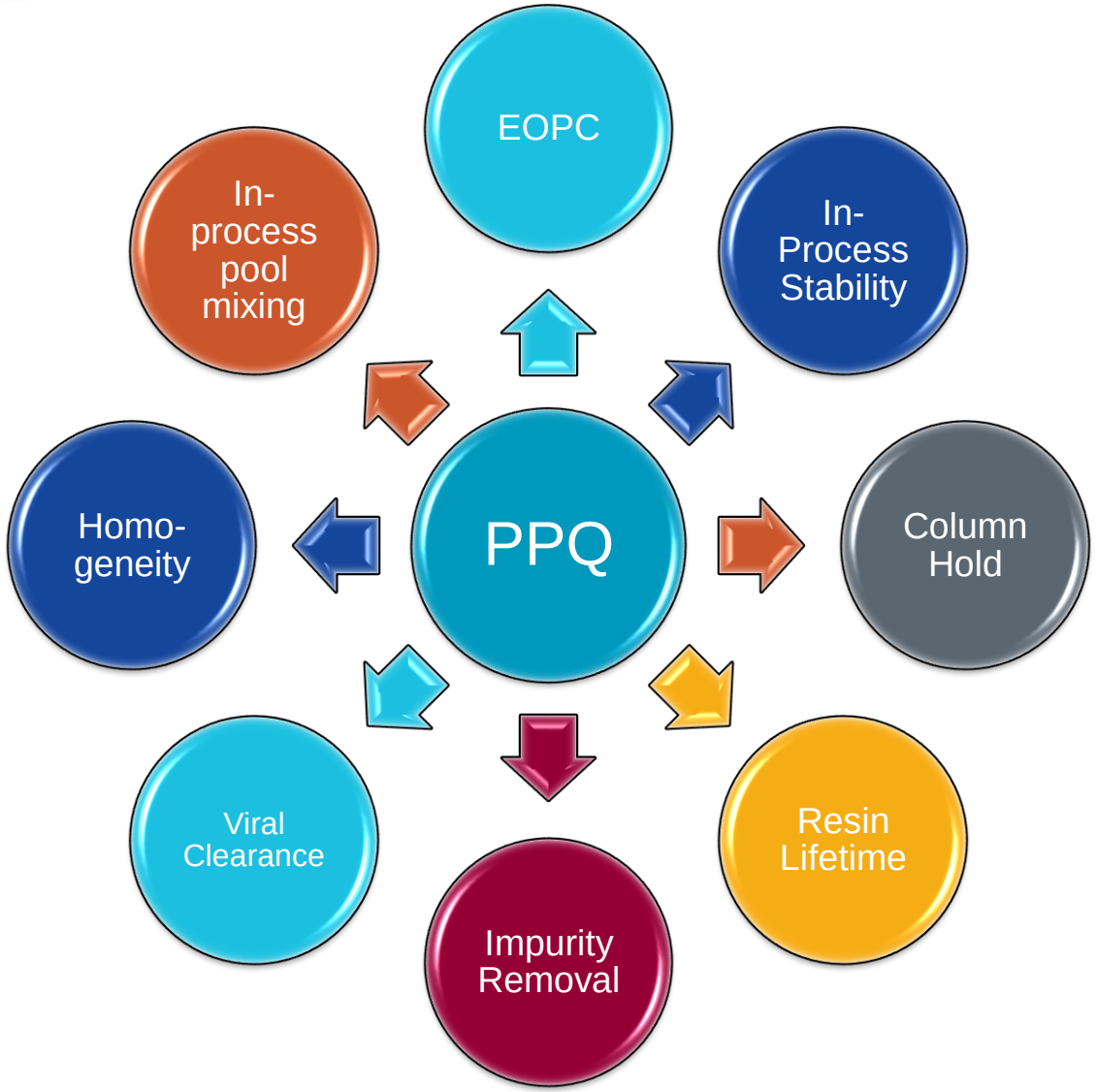
Downstream

- 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

Process Qualification
Focus on a Few Studies

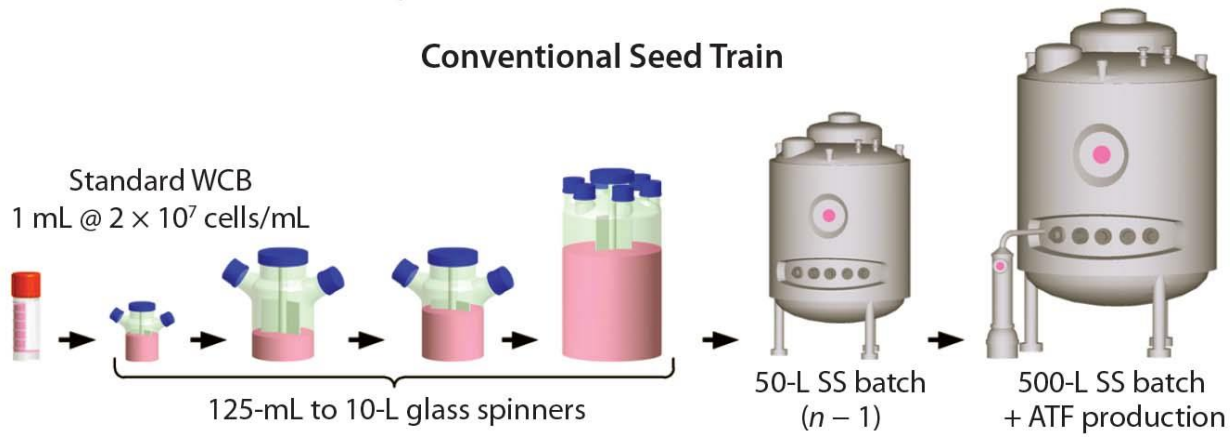


Challenges

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

Process Qualification

End of Production Cell Bank (EOPC) - To ensure that the genome of the source organism remains unchanged past the normal expected production



Back into inoculum vessels in MFG

Additional Generations

Bank

Back into inoculum vessels/ mock reactors in PD

Additional Generations

Bank

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

Process Qualification

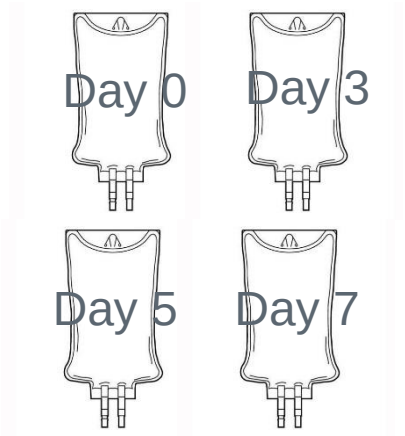
In Process Hold - To ensure the biochemical nature of the product does not change over a defined hold time and microbial ingress does not occur during the hold

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**

Process Qualification

Column Carryover - To ensure that product from previous lots does not carryover (cross-contaminate) the current batch

Small-Scale

Feedstock from GMP
Or applicable scale-down model

Test for
product carryover and
impurities as needed
throughout the lifetime

MFG-Scale

Feedstock from GMP

Test for
product carryover and
impurities as needed
throughout the lifetime

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**

Process Qualification

Viral Clearance (P3) - To demonstrate viral clearance against 4 types of viruses

Phase 1

Feedstock from GMP
Or applicable scale-down model

2 viruses (MMV, XMulV)
- In duplicate

Test for viral removal

Phase 3

Feedstock from GMP

Additional 2 viruses (MMV, XMulV, Reo3, PRV)
- In duplicate

Test for viral removal

Process Qualification

Viral Clearance (P3) - To demonstrate no viral carryover.

Phase 3 - Carryover

Feedstock from GMP

4 viruses
(MMV, XMulV, Reo3, PRV)
- In duplicate

Test for viral removal

Phase 3 - Carryover

Feedstock from GMP

4 viruses
(MMV, XMulV, Reo3, PRV)
- In duplicate

Test for Carryover of Virus

Clean

Feedstock from GMP
Without virus

Process Qualification

Viral Clearance (P3) - To demonstrate that viral clearance does not change over resin lifetime

Phase 3 – Resin EOLR Prep work Option 1

Feedstock from GMP

Predicted # of cycles in GMP + additional

Execute until maximum lifetime

Phase 3 – Resin EOLR Prep work Option 2

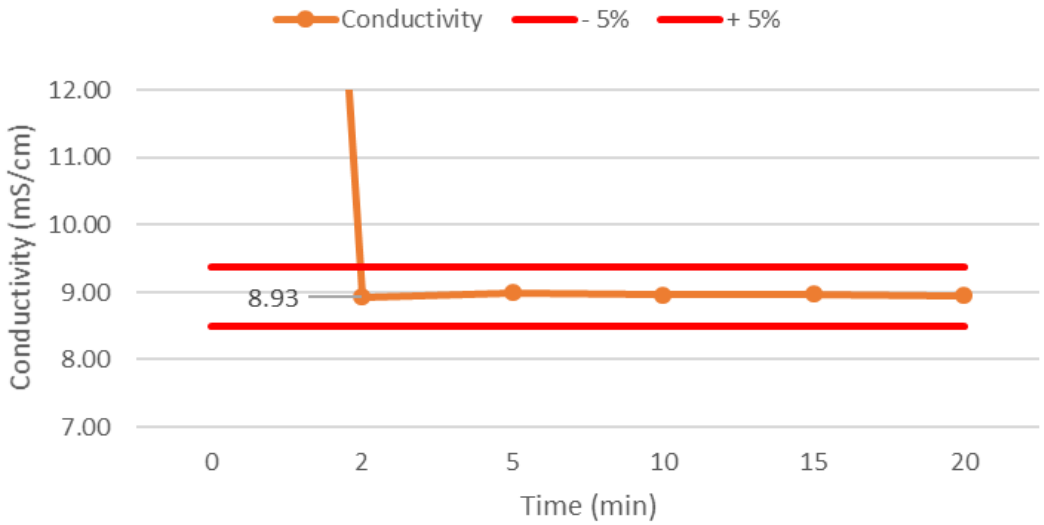
Feedstock from GMP

Execute until maximum lifetime → **Remove resin → pack in small columns → Execute Study**

Process Qualification

In-process liquid mixing - To confirm the in-process material is homogenous

Use water as surrogate solution
Spike with 5M NaCl
Measure conductivity



Process Qualification

Fill Homogeneity - To confirm the BDS fill process is homogenous

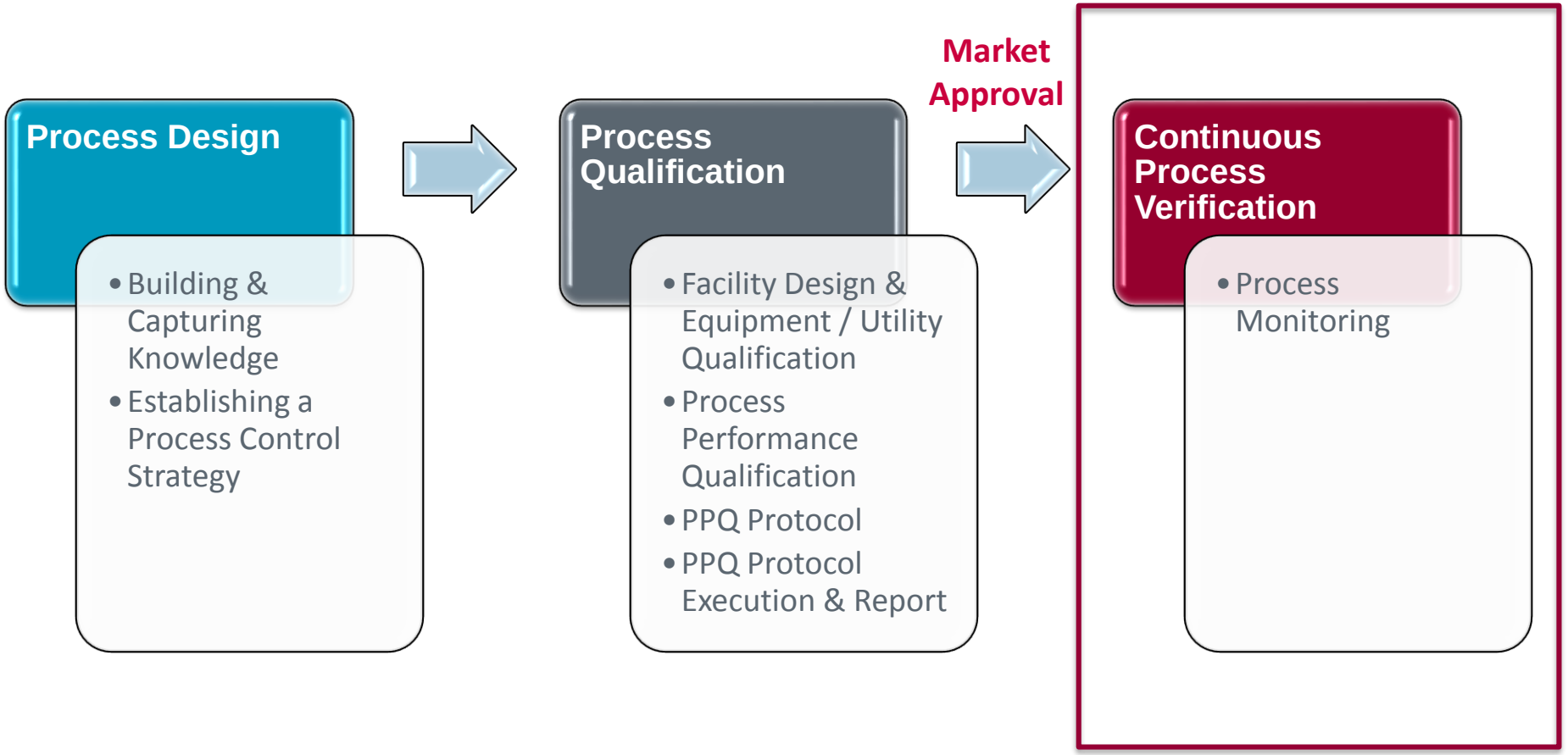
Fill into multiple containers (bottles, bags, etc)

Remove samples from beginning, middle, end

Test for protein concentration or other indicator

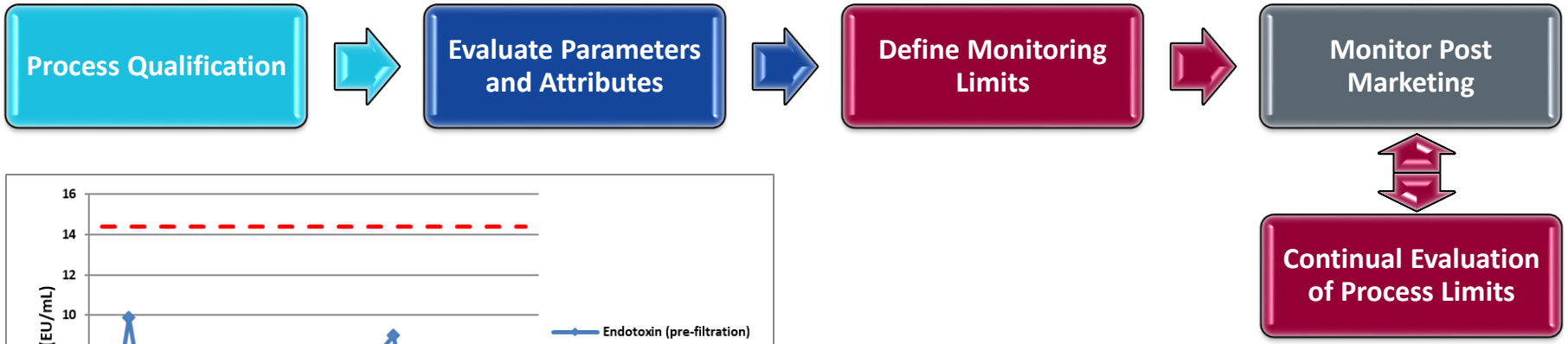
	Batch #1		Batch #2		Batch #3	
Sample Point	Protein Conc	Osmo	Protein Conc	Osmo	Protein Conc	Osmo
Before the Fill	10.47	258	10.31	255	10.27	255
Beginning	10.51	257	10.26	258	10.25	255
Middle	10.54	258	10.24	257	10.24	255
End	10.56	258	10.25	257	10.21	255
SD	0.04	0.50	0.03	1.26	0.02	0
Avg	10.52	257.67	10.27	257.33	10.24	255
% CV	0.4%	0.2%	0.3%	0.5%	0.2%	0.0%

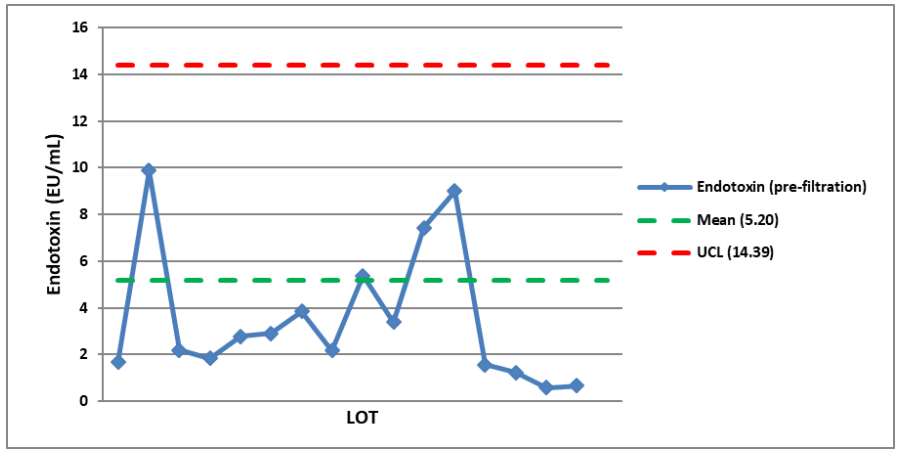
Avid's Process Validation Approach

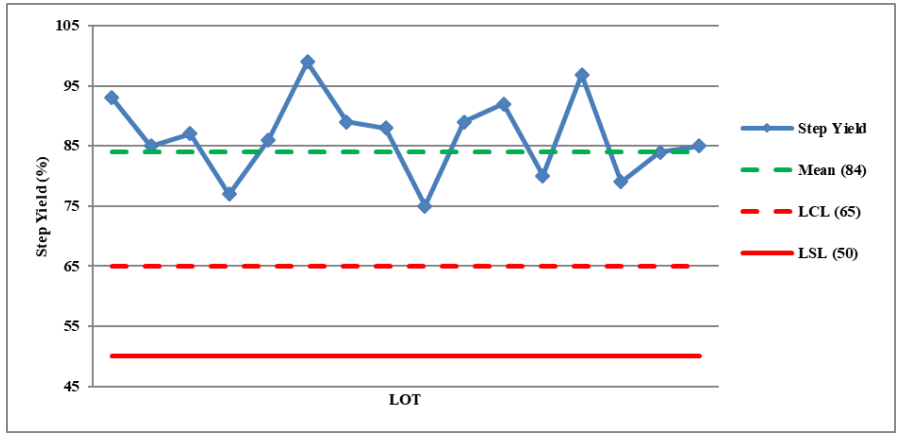


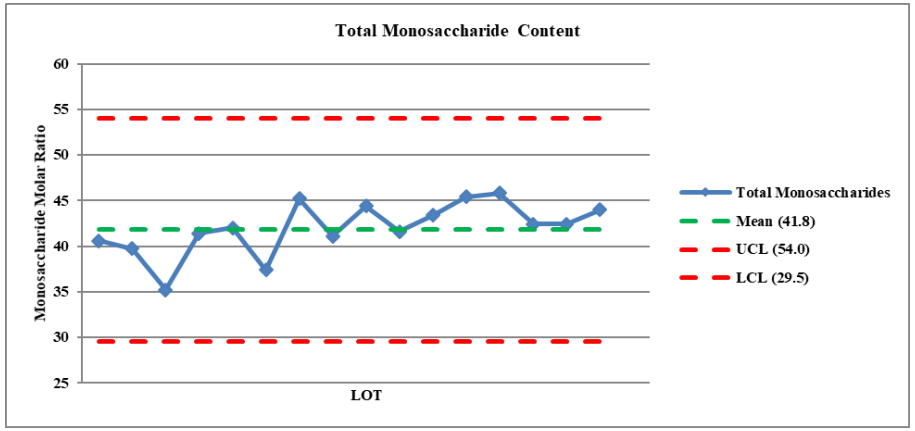
Continuous Process Verification

Ensures commercial process is in a state of control





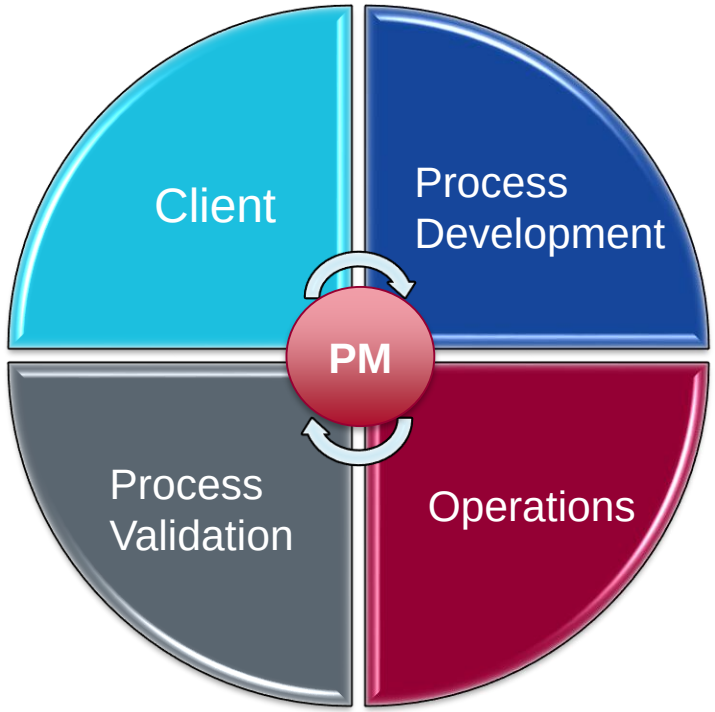




Key Factors for Successful Process Validation

Conducted 10 PPQ Batches Through Close Partnership with Internal and External Clients

- ✓ Proper Planning and Good Training of the Operations staff are the key of success
- ✓ Avid has a dedicated Process Validation team to oversee the technical and quality aspects of the campaign
- ✓ Avid has a dedicated Project Manager to ensure every step is completed per agreed plan and timeline



Thank you

Please come visit us at Booth #1159

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