CLARIFICATION
SCIENTIFIC CONCEPT TO ENGINEERING REALITIES

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Clarification Unit Operations

- Disc Stack Centrifuge
- Tangential Flow Filtration
- Depth or Normal Flow

Process Design / Parameters

- Centrifugation
  - Feed Rate, Backpressure, Bowl Speed, Discharge volume, Discharge Frequency
  - Type, Vendors, CIP, SIP

- Tangential Flow Filtration
  - Cross Flow Rate, Backpressure, TMP, Permeate Flow Control, Concentration Factor, Diavolumes,
  - Membrane Chemistries, Geometries, Vendors, CIP, (SIP)

- Normal Flow Filtration
  - Pressure, Flow Rate, # of Stages,
  - Filter chemistries, Geometries, Vendors, CIP, SIP
## Manufacturing Considerations

- **Process Design**
  - Scale Up (Reproducibility)
  - Robustness (Consistency)
  - Material Selection
  - Sampling Strategies / Data History
- **Equipment (Ancillaries)**
  - Reliability
  - Ruggedness
  - Cleanability
  - Maintenance (Time & $$)
  - Wear and Tear
  - Aseptic Sampling points
- **Quality / Regulatory**
  - Documentation
  - Training
  - CC / DEV / CAPA
  - Specifications
- **Supply Chain**
  - Assurance of Supply
  - Lot to Lot Variability
  - Vendor Changes
    - MFG Procedures
    - Raw Materials
    - New Configurations
    - Discontinuations

## Biologics Manufacturing

- **Contamination / Elevated Bioburden or Endotoxin**
- **Rouging / Pitting**
- **Debris / Unknown Residues**
- **Haze / Discoloration**
- **Deviations**
  - Incorrect Component (O-rings, gaskets, etc)
  - Carryover (Product, media, resin, etc)
  - Post Release
  - Not observed before (Low yield, high PRI, OOS etc)
- **Vendor Issues**
  - Changes in Raw Materials, MFG processes, configurations, discontinuations (Known) / Unknown
- **Equipment Breakdown / Probe failures**
- **Out of Control points, Shifts, Trends**
Filtration Case Study

- Blockage of 0.2µ filters
- Worked with Filter Vendor to identify / resolve issues
  - No Product change over / Line clearance procedure
  - Missing parts and misalignment of filter components
  - Filter media variability
- Problem was resolved after several months
  - Lack of aseptic sampling provision between filter trains
  - No Baseline data for turbidity of filtrate

Summary

- Process Design is a necessary first step
- Facility Design and Operation is key
- Vendor Management
- Data collection / Knowledge Management
- Scale Down Models
- All of the above play an important role in ensuring long term success during commercial manufacturing