CLARIFICATION
SCIENTIFIC CONCEPT TO ENGINEERING REALITIES

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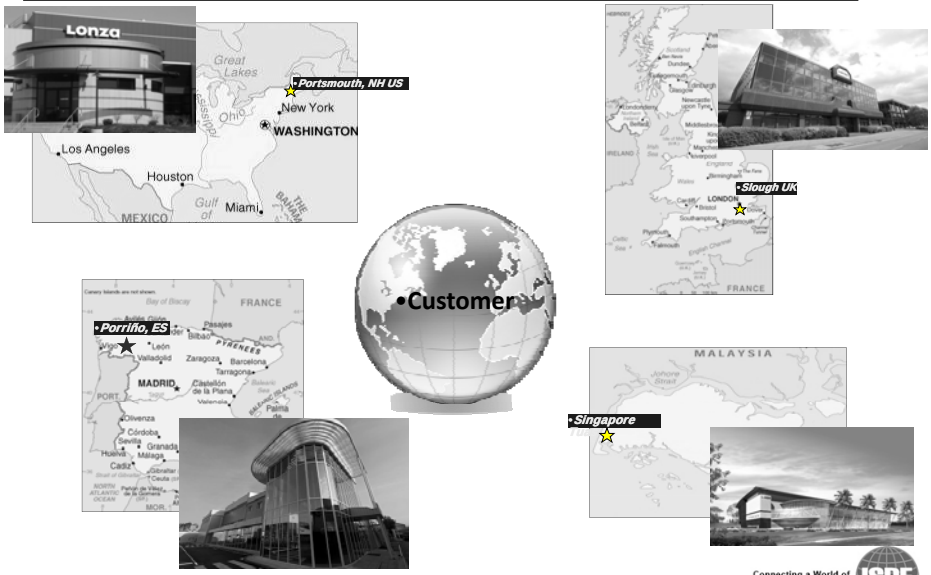
•Lonza Biopharmaceuticals - Mammalian Operations Sites Lonza



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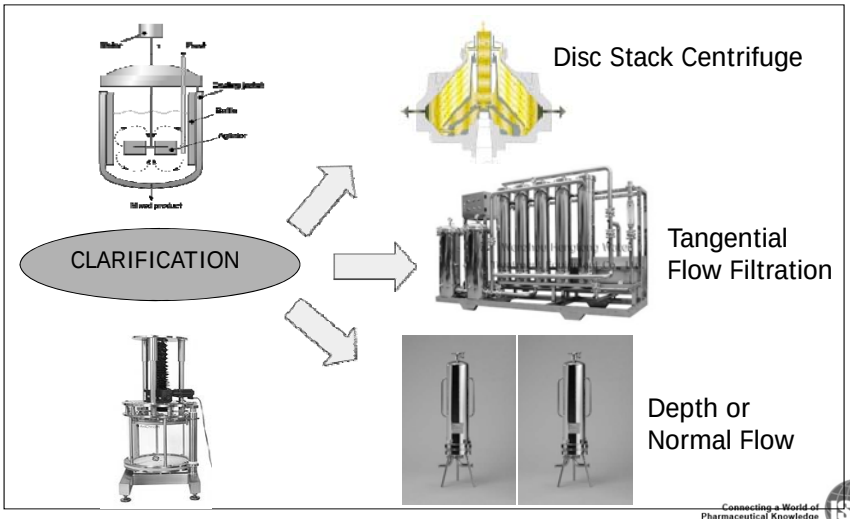
Clarification Unit Operations



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
    - Discontinuation

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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

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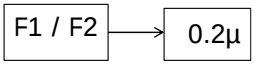
Filtration Case Study



- 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

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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

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