ENGINEERING CHALLENGES IN SCALING PURIFICATION FROM THE LAB TO FACILITY

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Topics

• Introduction
• Getting from lab to commercial scale
• Chromatography challenges
• Single Use challenges
• Filtration challenges
• Q & A
Scope of presentation

• Understanding of how to move a process from lab to large-scale
• Present challenges and solutions
  • All real life examples in validated facilities
  • No deep dives into separation theories or costs

A little about myself

• MS in Chemical Engineering
• 12 years in industry
• JNJ, Amgen, Wyeth, Genzyme
• ESC2, BioCork, AR5, WGC, 74CCE
• PD, Engineering (Equipment, Site and Project), Project Management, Operations
Typical Process Handoff

- Process Parameters
- Chromatography
  - CVs, pH, Conductivity
  - Linear velocities
- Filtration
  - g/m², flux, temperature
  - Flow rates, TMP
- Process-centric
- Implementation
  largely site specific

Typical Engineering Project

- Mass Balance
- Process Flow Diagram
- P&IDs
- Specs & Fabrication Docs
Where is the emphasis?

- Making the process work
  - Equipment Sizing
  - Performance / Recovery
  - Cleaning / Steaming
  - cGMP / Safety
- But… even after verification is complete, you don’t know everything about the system

Process needs to be integrated into the facility

- Interfaces can create unanticipated design challenges
- Conflicts in design philosophy, system demands, and layouts
Typical Large Scale Facility Scheme

Where can things go astray?

• The process parameters are well defined to give one set of performance criteria
• The rest are based on standards or heuristics
  • ISPE Baseline Guides / Good Practices Guides
  • ASME BPE
  • GAMP
  • CIP / SIP guidelines
• Often times, the support equipment will be the source of your largest headaches
Some Examples

- Chromatography
- Single Use Technologies
- Filtration

What’s the same, what’s different?
Typical Large Scale Manufacturing

Valve Manipulations on Skids

• Original design
  • 2” manual diaphragm valves
  •Disconnected from skid for buffer CIP
  • Contamination, Ergonomic, Safety issue
  • Lost time to operators moving between floors

• New design
  • 2 way divert valves
    • CIP port with hose to CIP return
    • Buffer feed stays connected

• 21 valves, $250,000 project (TIC)
Old Valve Configuration

Process Mode

- Buffer to Skid
- Process Waste

Cleaning Mode

- Buffer to Skid
- CIP Return
- To Washer

New Valve Configuration

CIP Return

- Buffer to Skid
- Process Waste

Connecting a World of Pharmaceutical Knowledge
Pictures of Chrom Valves

Large Scale Process Columns

- > 1.0 meter columns commonly seen in processing
- Protein A (2.0 m DIA)
  - Column itself > 10 tons
  - Additional weight of skid, resin, and buffer
- Ensure that floor loading calculations are performed for fully flooded column(s)
- Packed in place, keep in mind logistics and viral segregation
- Evaluate alternate materials
20% (v/v) Ethanol Storage Buffer

- Per NFPA, 20% EtOH = 1C Flammable solution
- During scale up, volumes of flammables must be considered
- Process rooms, buffer prep & hold, column packing may require explosion proof classification, fire water retention
- Investigate alternate storage buffers (e.g. buffered Benzyl Alcohol) or caustic stable resins

Single Use Implementation in Purification

- Mostly in buffer hold
  - Most bags cannot be pressurized
  - Must be staged close to unit operations
  - Best for ambient solutions
  - Metal beats plastic every time
- Avoid feeding unit operations from the top of a buffer bag
  - NPSH still matters
  - Pump suction may collapse tubing
Want to know the material flow? Follow the trail of destruction…

- 750 L buffer tote
  - 1650 lbs
  - 4 casters
  - ~206 psig / caster
- Use large casters
  - Autoclavable
  - Non-marking

Moving pallet tanks
Airlock and hallway sizes may be too small in existing facilities

Room height for storage totes

- 13 ft
- 12 ft
- 9 ft

- 2500 L
- 1500 L
- 1000 L
- 2 x 1000 L
What’s the same, what’s different?

• Large differences in tubing and piping
• Instrumentation & automation
• Congestion within the skid boundary
• Hold up volume

Filtration

• Recipes and control loops may not act they way you think they will
  • Pressure trapping = popped rupture disc = mess
• Drainability, Cleaning, and Steaming
  • Lots of extra piping and instrumentation
  • Places for pocketing and contamination
  • Routine operations and maintenance needs
• Filter bells are heavy, lifting devices and landing zones are required in process suites
Final UF/DF

- Product made in two sites
- Process change
  - 2x product mass at formulation
  - No changes to TMP / flow requirements
- One site reported a much lower Vmax of the BDS filter pool
  - 3x more filter area
  - Associated change in the BDS fill area

Site Differences On Final UF/DF

- 20 L hold up
- 1” skid

- A: 30 L holdup
  - 1st conc. & DF
- B: 7 L holdup
  - 2nd & Flush
What happened?

• Site A required a higher pump speed to maintain required TMP setpoint
• Diptube was not fully submerged at all phases of processing
• Protein aggregation through system that decreased filterability of BDS

How would two skids help?

• At site B
  • One skid dedicated to a fast initial concentration & diafiltration
    • Wider operating range of titers and volumes
  • Other skid has small hold volume for final concentration and buffer flush
  • Total process time less than Site A
  • No filter increase was required at Site B
• Platform purification process have wide variation in titers and BDS concentrations
Conclusions / Takeaways

• Common major issues at scale appear in interfaces between the process and support equipment
  • Usually after process validation is complete and routine operations are established
  • Appear as safety issues, contaminations, and repeated deviations
  • Process itself will usually be OK
• Problems scale with the process
  • Minor issues at smaller scale become huge issues at large scale
• Keep cleaning/steaming/maintenance in mind

THANK YOU FOR LISTENING!
Additional Slides

20% Ethanol – Backup Slide

- 200 cm x 30 cm column = 942 L CV
- 10 L shipper ~ 5 L resin / 5 L 20% EtOH
- ~190 containers = 950 L 20% EtOH
- 2 CVs = 1884 L 20% EtOH + Prep/Storage
- Flam1C = >22.8C & <37.8C, 36C
- Classification increases above 208 L for 1 vessel or agg. storage > 3785 L