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

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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

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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

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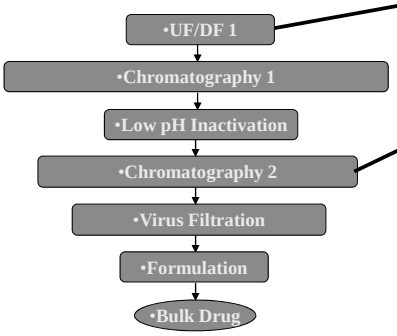
Typical Process Handoff



- Process Parameters
- Chromatography
  - CVs, pH, Conductivity
  - Linear velocities
- Filtration
  - g/m^2, flux, temperature
  - Flow rates, TMP
- **Process-centric**
- **Implementation largely site specific**

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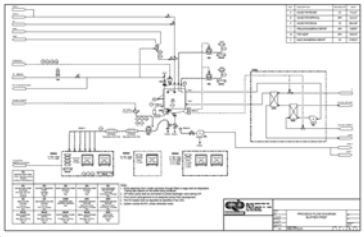
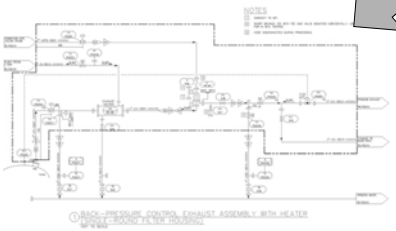
Typical Engineering Project

•Mass Balance



•Process Flow Diagram



•P&IDs

•Specs & Fabrication Docs

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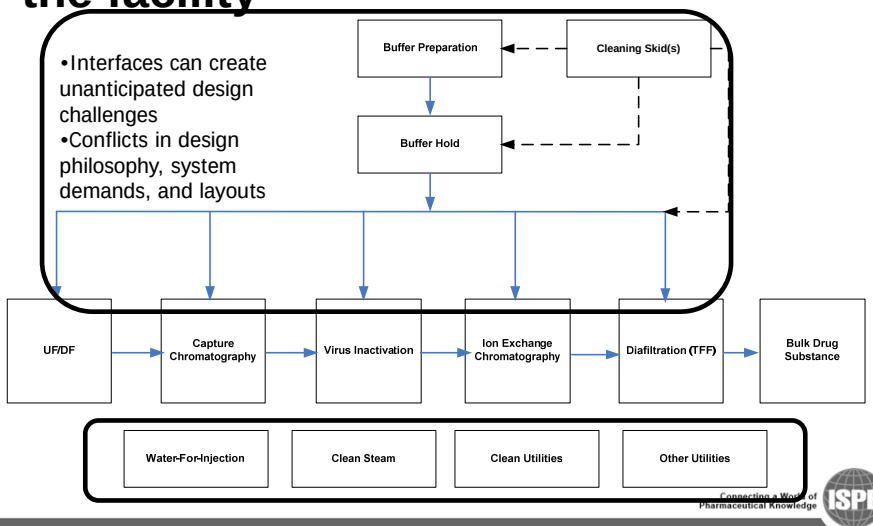
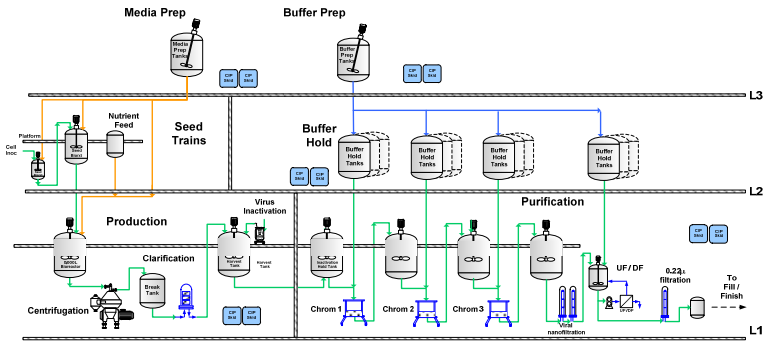
Where is the emphasis?

- 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



Typical Large Scale Facility Scheme



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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

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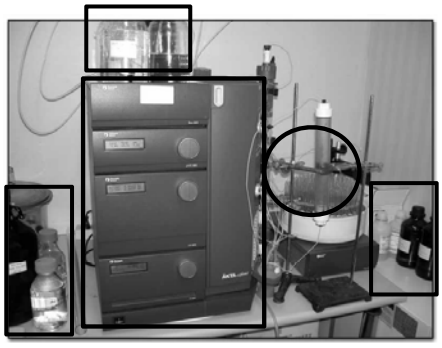
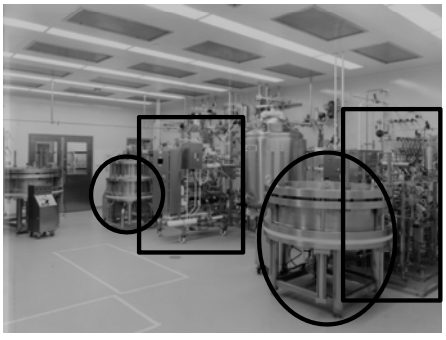
Some Examples

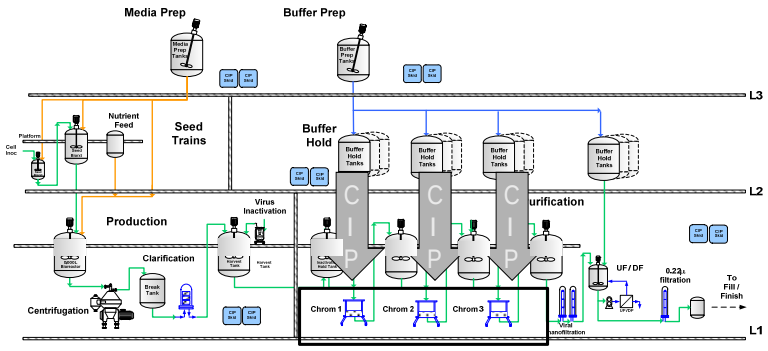
- Chromatography
- Single Use Technologies
- Filtration

What's the same, what's different?





Typical Large Scale Manufacturing



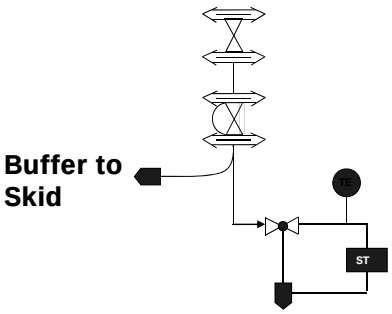
•Skid Sanitized

Valve Manipulations on Skids

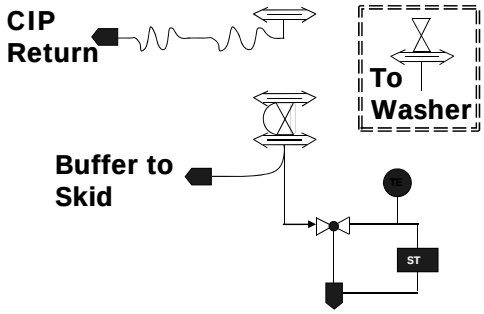
- Original design
  - 2” manual diaphragm valves
  - Disconnected from skid for buffer CIP
  - Contamination, Ergonomic, Safety issue
  - Lost time to operators moving between floors
- New design
  - 2 way divert valves
    - CIP port with hose to CIP return
    - Buffer feed stays connected
- 21 valves, $250,000 project (TIC)

Old Valve Configuration

Process Mode



Cleaning Mode



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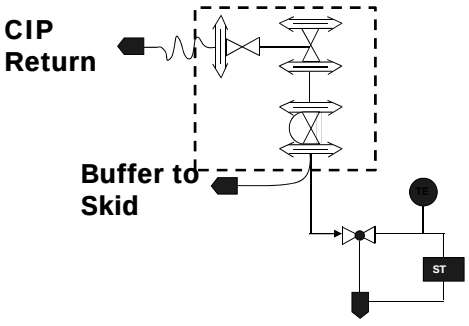
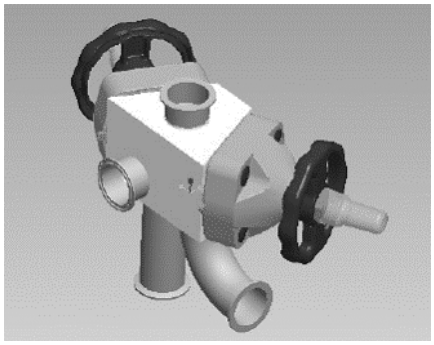
New Valve Configuration





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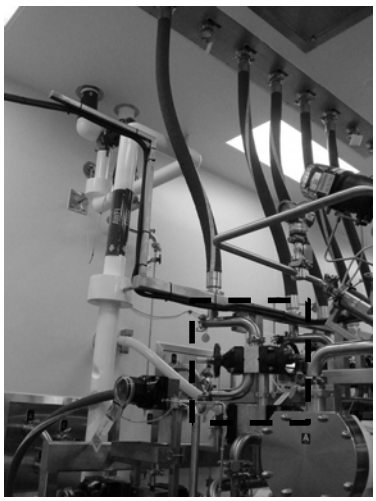
Pictures of Chrom Valves



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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

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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

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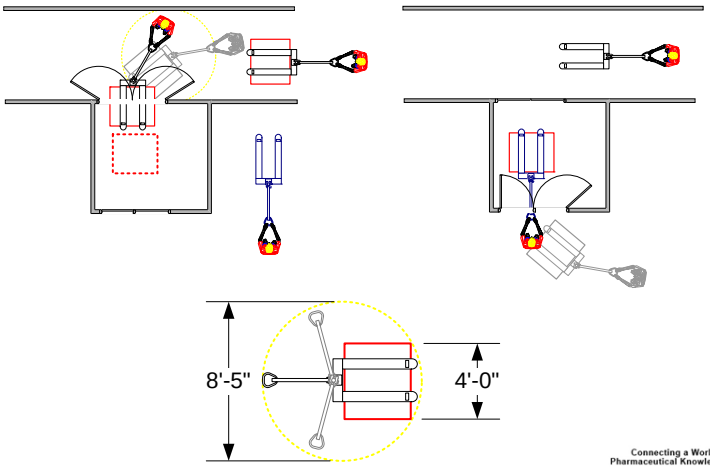
Moving pallet tanks



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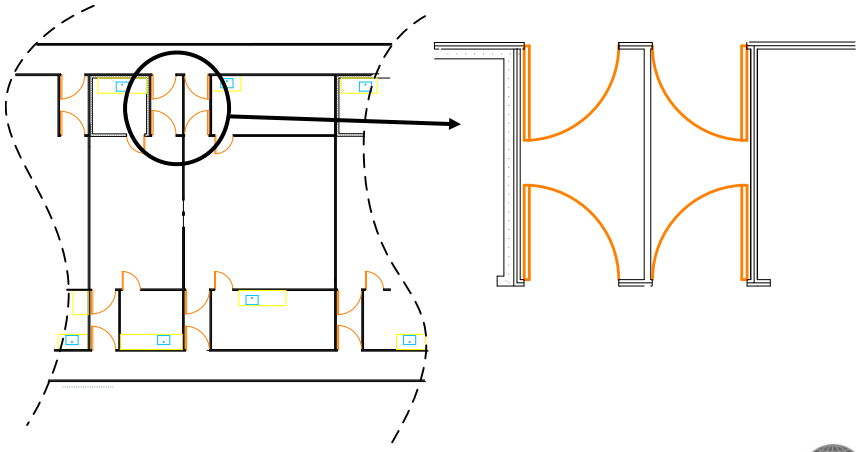
Airlock and hallway sizes may be too small in existing facilities



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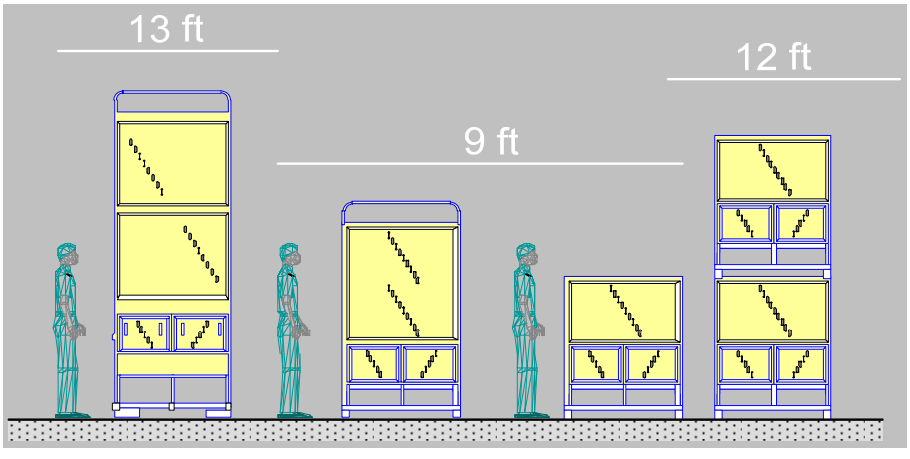
Room height for storage totes



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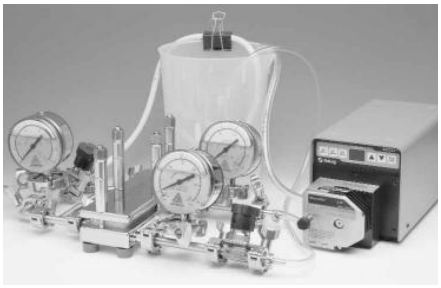
What's the same, what's different?



- 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

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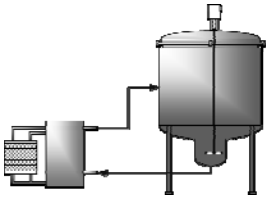
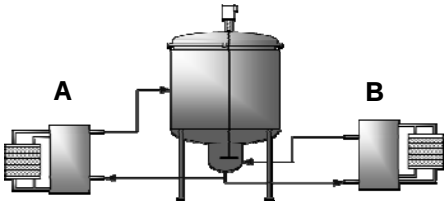
Final UF/DF

- 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

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THANK YOU FOR LISTENING!

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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