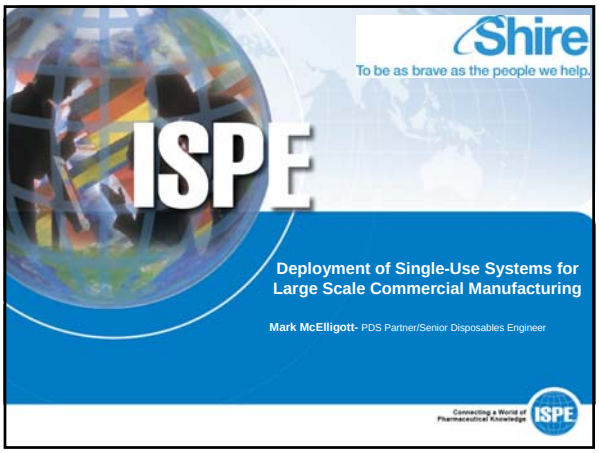


What was one of the biggest Industry catch phrases in last decade?

"We're Going Paperless"

- How did that idea and implementation work out?
- What were some of the biggest challenges for a full roll out of implementation?

What is the newest industry catch phrase regarding SU Systems?

"We are going completely Single-Use in MFG"

- But how ready are the Suppliers, Sub-Suppliers, Quality Systems, Process Engineers, etc to meet the challenges of a fully integrated Single-Use Manufacturing Facility?

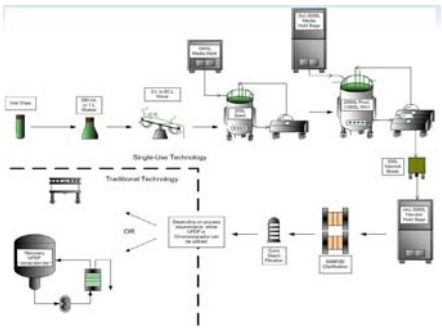
SU System Implementation in GMP Production

- In the Single-Use Implementation Realm, the acronym PD stands not only for Process Development, but more importantly **Product Development**

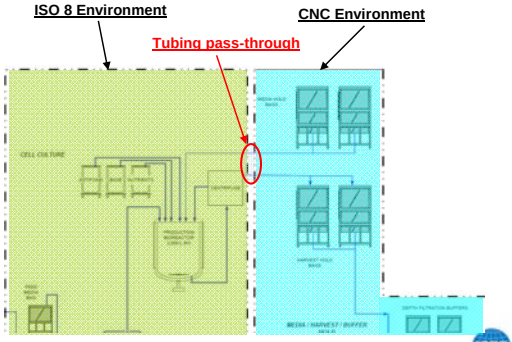
Outline

- High Level Facility Overview
- Single Use Scale Up Process/Technical Challenges and Risk Mitigation Plans
- Single-Use Supply Chain and Quality System Challenges and System Development

Disposable Facility Overview



Single Use – Facility integration



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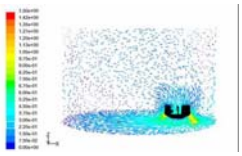
Single Use – Process Challenges

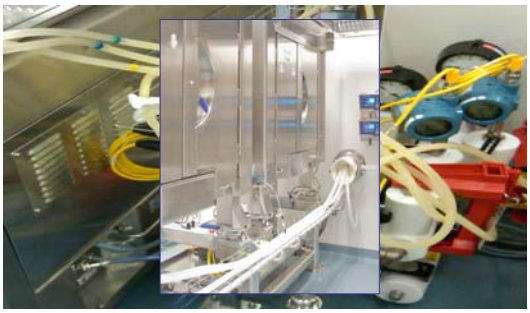
- Material transfer
  - Tubing sizes limit flow rates
- Heat transfer
  - Plastics are poor conductors, large scale implications
- Mixing
  - Proprietary mixing devices not as well characterized as their traditional counterparts (Np, shear)
- Scale
  - Some technologies scale better than others



Single Use – Design Challenges

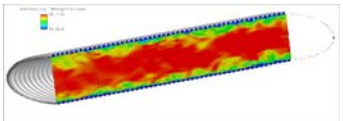
- **Technology** – constantly changing capabilities of existing systems, new technologies evolving to address Single-Use needs however some are largely untested and therefore the risks are not fully vetted
- **Robustness** – What may work for a 3-5 day process may not work for a 30 day process. Ensure the consumables design meets minimum processing requirements
- **Consumables** – facility design must incorporate consumable design to lower the degree of risk.
- **Procurement** – Hardware must dovetail with "soft" wares
- **Disposal of disposables** – consider the alternatives for decontamination and waste management early
- **Safety and Hazards** – bags/tubing not pressure rated, limited containment options.
- **Draining** – flow rates are painfully slow, consider dedicated drain ports
- **Consumables Transport -** especially for frozen single-use components
- **Tubing management** – requires thoughtful consideration

Do you see anything wrong here?



Fluid Flow Dynamic Challenges and Mitigation

- Q: When did tubing slopes, runs, elevations, etc become unimportant?
- A: Never. SU tubing has been thought of by several companies as "if you don't need to clean it, then there is no impact if it takes 40 turns, and sags" which is just not the case. Fluid flow and general hydraulics are still very important.
- Consistency of SU installation (tubing trays) and Secondary Inspection (Fluid Flow dynamics and engineering principles)



Risk Mitigation Strategies

What is a sandbox?

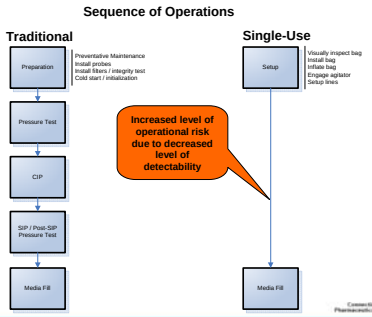
- Fully installed production prototype
- Fully automated with actual I&C
- Staffed by engineering and operations
- Full batch capabilities
- Off-site
- All consumables available for testing

Sandbox - Benefits Realization

- Process integration performed on 1st batch of equipment before replication
  - Large number of performance studies (mixing, temperature mapping, mass transfer) completed
  - Uncovered a process issue that would have delayed the startup by months if discovered after installation in plant
- Functional performance testing at scale with full controls in place
  - FAT execution for individual systems
  - Remedied over 2000 automation and I&C issues
- Utility requirement verification for early balancing of utilities
- Operational shakedown of all procedures and batch records
- Ancillary equipment testing such as welders and sealers, carts, waste totes, etc. Consumables design verification
  - Design and specifications finalized before “mass” production
  - Facilitated design and pre-fabrication of custom cabling and tubing management systems
- Hands on training long before facility construction is completed
  - Provided months of operator training opportunities on actual working equipment
- Off-site location provided extra focus vs. plant startup environment

Single Use – Operational Challenges

Higher Equipment Risk for Operations:



Connections and Integrity Challenges

- System Integrity (Leak Detection and Integrity Testing of bags and filters)
  - How many tubing welds per 30 day run in a completely single-use upstream manufacturing process?
    - A 3-5 minute STW replaces the need to Clean, Pressure Test, Steam and Hold under pressure. This needs to be treated as a program with qualification and verifications rather than a quick task. It must not lose its importance.
  - Integrity Testing must not compromise bag integrity or risk damaging internal components where applicable


Single Use – Technological Challenges

- Gamma Irradiation Impact to all different types of materials
- Technology Limitations with Sterile Tubing/ Welding/ Sealing
- Technology Limitations with Single-Use Sensors
- Confirmation of Single-Use really being Single-Use



Holistic Understanding of Gamma Irradiation

- The industry understands Gamma Irradiation from a Sterility/Microbial challenge capacity very well

So what is the problem?

- What the industry does not fully understand is the impact of Gamma Irradiation on the properties of different materials of construction
  - Why does ZrO_2 turn Purple and what is the physical impact?
  - What is the impact of the shadowing effect of SS?
  - With multiple forms of HDPE (for instance), what structural and morphological changes occur to an HDPE at 30 kGy versus 40 kGy and does this put our equipment/process at risk?

Technical Limitations

- Sterile Tubing Welding/Sealing, SU Probes/Sensors
  - VCD?
  - Long Term pH?
  - DO2? Temp?
  - Pressure?
  - In-line sampling?
  - Wet Welding?
  - Welding Large Tubing Diameters?
  - Max ACD/DAC Sizes?

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What is an acceptable rate of failure from SU Suppliers?

0%

What is the success rate expectation of MFG on their SU components?

100%

SU Supply Chain Necessities

- Supply agreements must cover suppliers and their sub-suppliers' supply chain for all critical components and equipment
- Supply chain must be a partnership where solutions are developed and tested together for continuous improvement
- Any change to a SU component must be communicated, no matter how small your supplier and their sub-suppliers believe the change is
- Must establish ground rules for delivery and any needed future modifications
- Must develop an effective URS for all single-use systems

Supplier Agreements to consider the following

- Mutual agreement for all critical quality systems
  - Supplier and Sub-Suppliers must operate as an extension of your Quality Department and follow the same Culture of Quality

You can not outsource Quality

- Must be able to audit in a similar unannounced fashion to ensure agreed to standards are being maintained at all times.
  - This arrangement will allow for a mutual understanding on the need for consistency in all assemblies, components and sub-components

Transition of the Process Engineer for SU

- Traditional Process Engineer with heavy expertise in:
  - CIP
  - SIP
  - Product changeovers
  - Fabrication of stainless steel systems
  - Knowledge of sanitary connections/couplings primarily for cleaning and sterilization
- In contrast, single-use system engineer requires:
  - In depth understanding of polymeric materials (chemical/physical properties)
  - Familiarity with leachables / extractables
  - Fabrication methods for plastic systems (molding, machining, welding)
  - Knowledge of aseptic connection devices (ACD)s for sterility
  - Knowledge of gamma irradiation and its impact to material
  - Familiarity with supply chain and vendor quality management

Redefinition of "Maintenance"

- Engineering input to front end Technical Quality/Supply Agreements with focus on:
  - Consistency of supply
  - Lead times
  - Change management
- Engineering is an integral part of:
  - Vendor change notice review boards
  - Vendor audits
  - Supplier management forums
  - Failure Investigations
- Reliability is a function of supplier consistency, reproducibility and repeat quality assurance
  - Vendor must have sampling regimes to ensure critical aspects of their SU components and sub-components

Conclusions

- Use of disposables at a commercial scale is a reality but somewhat limited beyond the clarification process
- Single-use systems provide significant benefits from a time, raw material use, number of operations personnel, etc, but be ready to face a variety of technical and quality challenges
- Many of the challenges can be overcome by strategic planning to incorporate SU components and sub-components in process and facility design, developing effective quality systems to ensure consistency of the supply chain, and developing risk remediation practices to ensure consistency/repeatability of all processing requirements

Questions?