UNCOVERING HIDDEN COSTS BEHIND IMPLEMENTING EFFECTIVE SINGLE USE TECHNOLOGY

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EFFECTIVE SINGLE USE TECHNOLOGY IMPLEMENTATION AND INTEGRATION

TYPICAL PROMISES AND PITFALLS

Some High Level Promises of Single Use Technology (SUT)

- Reduced dependence on raw materials such as Water for Injection, Cleaning Chemicals, Clean Steam, etc.
- Reduced processing durations and on floor support for cleaning and sterilization operations
- Reduced costs surrounding cleaning and sterilization validation
- Increased Flexibility due to Non-Product Dedicated Equipment
- Lower Up front Investments (50% savings in Capital Investments and up to 30% savings in operational costs) and quicker project durations due to a reduction of facility "hardware"
- Lower Risk for Cross Contamination
- Reduced Equipment Maintenance

BUT AT WHAT COST?

Typical Single Use Implementation Pitfalls

- Not establishing requirements relative to the SU components and characterization
- Not having the manufacturing sciences or process development experience to dictate the criticality of requirements
- Not understanding the relationship between the SU components characterization and what is relevant to your process requirements
- Not having an effective Technical Quality Agreement (TQA) that establishes a partnership
- Not having a dedicated cross functional team to manage all aspects of a lifecycle approach including Vendor Change Notifications (VCNs) for SUT

Typical Single Use Implementation Pitfalls Continued

- Trying to use/transition a traditional process engineer in a SU Engineering role
- SU Suppliers who do not take ownership over their part or sub-components if there is a non-conforming material
- Lack of secondary SU suppliers for critical SU parts
- SU Supplier lack of knowledge behind what they are stating as characterized SU data
- Not establishing supply chain from a consolidated list of suppliers based on Business, Technical and Quality auditing

Typical Single Use Implementation Pitfalls Continued

- The variation level in the quality of information provided by SU suppliers
- Lack of tracking each SU part down to the sub-component level and where each part is used
- Mixed Interpretation of characterization data through contradictory statements provided by SU suppliers
- Lack of physical/mechanical and functional testing performed by suppliers
- With the process stream now more visible, greater scrutiny during visual inspection

<u>You Cannot Outsource Quality!</u>

EFFECTIVE SINGLE USE TECHNOLOGY IMPLEMENTATION AND INTEGRATION

COSTS TO BE PLANNED/ANTICIPATED

Effective SUT Implementation and Integration Costs

- **SU Implementation cannot be something that is a side effort without a dedicated team or it is doomed to fail.**
- **A SU program/policy that establishes cross-functional requirements must be developed as the basis for implementation.**
- **SU Systems need to align with the program/policy and data driven to meet the process requirements**
- **Guidance from Process Development is required in terms of setting limits on characterization for items such as USP <788>, Extractables, USP <85>, USP Class VI, etc.**

New Planned/Anticipated SU Costs: Cross Functional Team

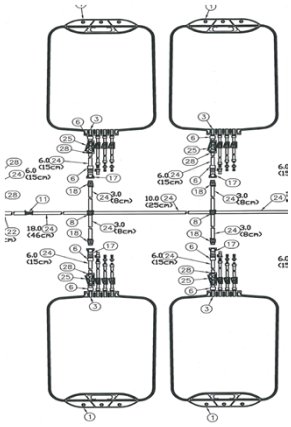
A Cross Functional Team Dedicated to SUT and the systems required to Manage:

- **Vendor Change Notifications**
- **Supply Chain Management**
- **Vendor Quality Auditing**
- **Non-Conforming Material Disposition**
- **Product Characterization Claims relevant to the End Users Process Requirements**
- **End User Initiated SU Part Changes**
- **Change Control, CAPA, Investigation, etc**

New Planned/Anticipated SU Costs: Subject Matter Expertise

Atypical Pharma/Biotech Process Engineering Expertise focused in the following:

- **In depth knowledge of polymeric materials (chemical and physical properties)**
- **Familiarity with Extractables and Leachables**
- **SU Component fabrication methods for plastic systems (injection molding, machining, welding, etc)**
- **Knowledge of Sterile Tube Welding, Tube sealing and Aseptic Connection devices to maintain sterility**
- **Knowledge of gamma irradiation and the impact to the MOCs used in the process**
- **Knowledge of supply chain and vendor quality management including industry guidance requirements relevant to process requirements**



Effective SUT Implementation and Integration Costs: Characterization including Extractables and Leachables

- Characterization data, including Extractables and Leachables must be included for both cost and schedule impact.
- Data from the components (sub-components) should be assessed against the process requirements and based off of where the highest level of risk to patient safety/product quality exists.
- Design Review/Risk assessment process whereby you design/review the SU component capabilities against the process requirements and assess any associated risk.

EFFECTIVE SU IMPLEMENTATION AND INTEGRATION

HIDDEN COSTS

Uncovering Hidden Costs: Overview

- VCNs
  - Raw Material Changes
  - Manufacturing Site Change
  - Product Discontinuation
- Non-Conforming Materials
- Establishing Secondary Supply Chain
- Managing Secondary Supply Chain
- Managing Custom Supply Chain
- Vendor Technical and Quality Auditing
- Vendor Quality Lapses
- Supply Chain Shortage
- Disposal

Uncovering Hidden Costs: Vendor Change Notifications (VCN) for Raw Material Changes

<u>VCN Impact Case Study:</u>

- Critical Supplier changes bag film material of construction.
- Bag is used across all products and sites for end user.
- Vendor Change impacts 40 parts with over 200 instances of use.

<u>Potential Impact and Associated Costs:</u>

- Based on the use, the end user needs to perform updated extractables testing and subsequent leachables evaluation
- Associated Change Control efforts
- All Custom DWGs need to be revised and incorporated into material/purchasing spec
- All Characterization needs to be reassessed against the process requirements

Uncovering Hidden Costs: Vendor Change Notifications (VCN) for MFG Site Change

VCN Impact Case Study:

- Critical SU Supplier changes manufacturing site
- SU Component are used at 1 site and across all products
- Vendor Change impacts 26 parts with over 90 instances of use.

Potential Impact and Associated Costs:

- New manufacturing site needs to have an vendor quality audit performed
- Depending on the level of observations new site may have remediation and subsequent remediation activities to manage.
- Could impact manufacturing operations impact due to supply chain concerns
- If the product is delivered sterile, the facility will need to perform baseline bioburden data for ISO 11137

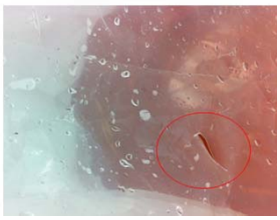
Uncovering Hidden Costs: Non-Conforming Materials Inspection and Disposition

NCMR Impact Case Study:

- Critical SU parts inspected and found to have a potential integrity risk
- Other SU parts from the same lot are inspected and found to have a similar issue
- Based on where this part is used (downstream of viral clearance) risk to the product is deemed too high

Potential Impact and Associated Costs:

- Effective and Relevant Training needs to establish real and meaningful failure criteria for visual inspection.
- Cost of all of the SU parts should the lot be compromised
- Failure disposition and root cause analysis for end user, in addition to gathering the critical/pertinent storage/handling data
- Associated Deviation, CAPA and Change Control Cross-Functional support



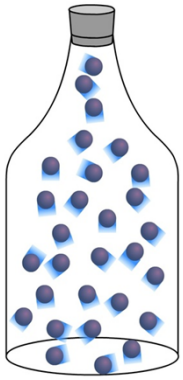
Uncovering Hidden Costs: Visual Inspection Non-Conformities

Particulate Case Study:

- An intermediate product bag is filled with process intermediate. While filling, the manufacturing technician notices an unidentified black particulate inside the bag.
- Forward processing is halted, floor support and QA are called in to make processing decision
- Since particulate is unidentified, batch is sent to drain and investigation commences to determine root cause

Potential Impact and Associated Costs:

- Processing run sent to drain.
- Particulate is sent out for analytical analysis to determine it's chemical make up.
- Investigation team performs root cause analysis – determined to be from bag
- SCARs issued to vendor to identify corrective action. Depending on End User satisfaction for cause audit might be warranted



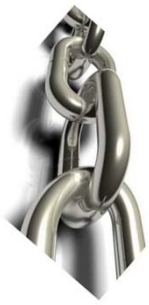
Uncovering Hidden Costs: Secondary Supply Chain

Secondary Supply Chain Impact Example:

- Critical SU Supplier provides 15 VCNs in 1 calendar year
- End User decides to transition to secondary supplier after never purchasing like for like components from them

Potential Impact and Associated Costs:

- Secondary supply chain needs to be reestablished with SU supplier since they put the product on hold due to end user not purchasing it for over 3 years.
- Secondary supplier needs to provide any VCNs associated with this part for review.
- Secondary part drawing needs to be reviewed for sizing, MOCs and dimensional accuracy



Uncovering Hidden Costs: Custom Supply Chain

Custom Supply Chain Impact Example:

- Critical SU Supplier provides 1 part that is their own IP with no secondary suppliers
- SU Supplier manufacturing site has critical vendor quality audit observations and end user is unable to use their products until remediated due to product /patient risk

Potential Impact and Associated Costs:

- Critical supplier can shut down manufacturing since their SU component is used on their equipment and they only have a single source supply chain.
- Attention to the critical observations and management of the remediation activities for both QA and Eng.
- Remediation testing analysis and sign off for approval for continuation of supply chain.
- Establishment of a secondary manufacturing site with similar capabilities. Requiring vendor quality auditing support.

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CONCLUSION

Uncovering Hidden Costs Conclusion

- **Program:** Must have a developed plan relevant to your site and process requirements
- **Personnel:** Must have a dedicated cross functional team focused on SU program management
- **Contingency:** Must have contingency planning and the understanding that SU suppliers will have changes and they should be managed through a mutual understanding that is outlined in the TQA.
- Single Use Implementation does have a number of distinct benefits when managed effectively. Understanding the deliverables, requirements and ultimately the up front costs to manage an effective SU program will result in better ability to forecast associated costs.

Uncovering Hidden Costs Behind Single Use Technology

Contact me with further questions:

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