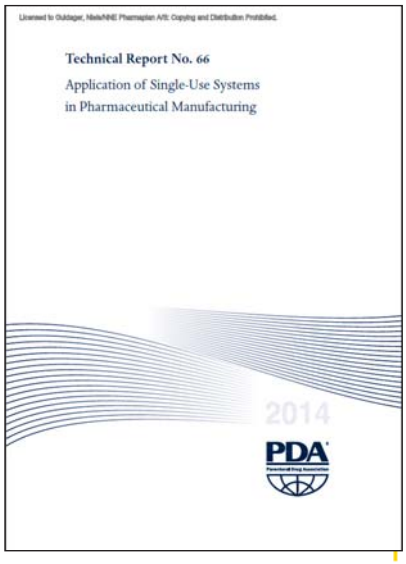
Case Study: Conversion from stainless steel to single use system

Backdrop: PDA Technical Report 66: Single Use Systems



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Purpose

Share example:

- Real life case considerations for conversion from stainless steel to single use systems
- Introduction and reference: PDA Technical Report no. 66 Application of Single Use Systems in Pharmaceutical Manufacturing

Outline

- Case scenario
- Reference PDA TR no. 66…single use systems
- Why change from Stainless to Single Use?
- Feasibility, Process risk, Product risk
- Results and Summary

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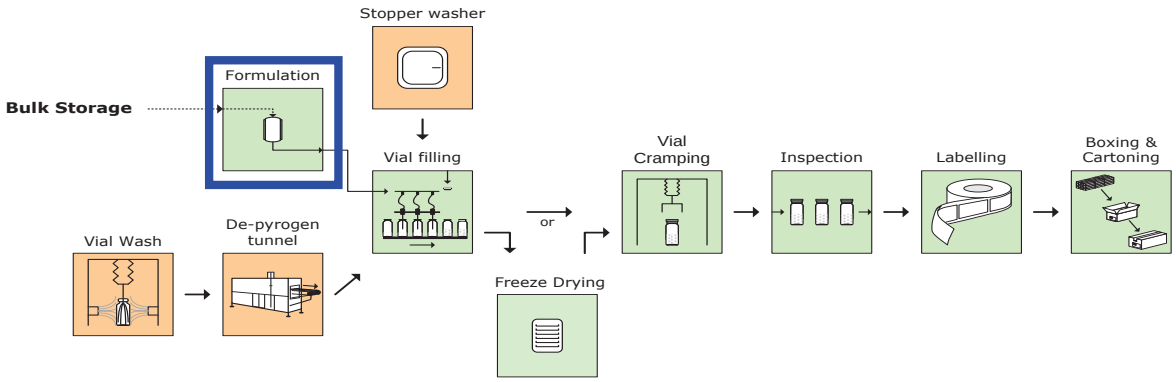
Case scenario: Formulation 1000L scale

- 1000L mobile formulation tank
- Grade C environment
  - Add WFI
  - Charge in solid form (powder) drug substance
  - Dissolution (agitation)
  - Add WFI
  - In-process-controls
  - Sterile filter to hold tank

Generalized Fill-finish flow
Formulation step starts aseptic process

- High risk step: no subsequent removal/purification
- Any impurities or contaminants will reach patient



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Typical challenge

- Products already in commercial phase
- Current stainless technology capabilities and limitations well known
- Advantages of single use systems evident
- Task: Determine potential of single use systems for current and future products

Technology examples: Stainless steel preparation vessel

- Stationary or mobile
- CIP/SIP or COP/SOP

Pharmaceuticalonline.com

IAE Pharma

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Technology examples: Single use mixing systems

Millipore

Thermo Fischer

GE Healthcare

Technology examples: Single use mixing systems

Sartorius

PALL

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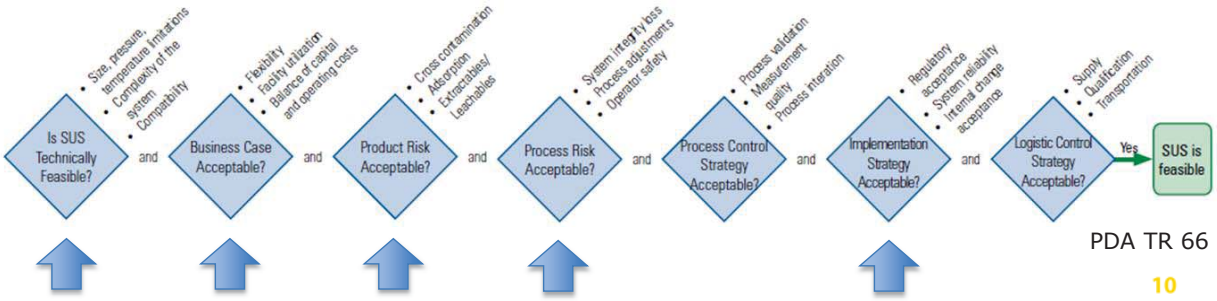
PDA Technical Report no. 66

Application of Single Use Systems in Pharmaceutical Manufacturing

- Suggested single use system decision pathway
- Structured approach reflected in report chapters
- Comprehensive reference for evaluation
- Arrows: focus for this presentation



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Why change: strategic advantage

- Strategic asset: manufacturing network flexibility increase
- **Benefit:** single use technology decouples formulation step from installations
- **Requirement:** compatibility demonstration – product and process

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Why change: economics

- Stainless steel technology, limitations:
  - CAPEX:
  - Investment cost (high finish surface)
  - Storage space (large number of tanks)
  - OPEX:
  - Mobile tank life cycle logistics: ready, in use, used, cleaning, service, clean/ready, expired…

Why change: quality aspects

- Stainless steel technology, limitations:
  - Visual check of dissolution
  - Visual check of powder residues on tank wall
  - Visual inspection of cleaning efficiency
- Note: limitations not necessarily realized but do represent lasting theoretical risk even with optimized sight glass and tank design

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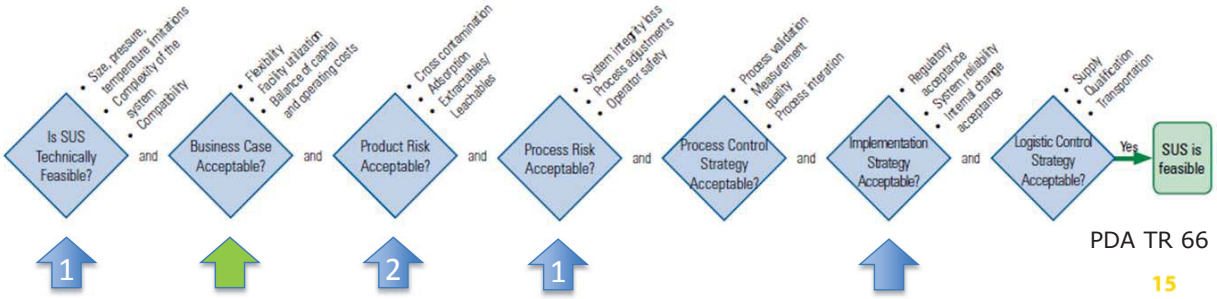
Why change: time aspects

- Stainless steel technology, limitations:
  - Cleaning operation documentation
  - Operator ergonomics (transportation)
  - Airlock/cleanroom transfers
  - Logistics (tank ready status and documentation)

Case approach – reference PDA TR 66

- Technical, process and product risk focus
- Business case implicitly demonstrated by flexibility potential and "1 bag vs. 1 mobile tank"
- Process testing very visual – provides up front stakeholder management value



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Process risk test approach

- Testing in 1000L scale - pilot plant environment
- Complete systems from single use suppliers
- Single use supplier support for initial setup and operator instruction
- Actual drug substance powder (expired, non-relevant quality defects, not for market)
- Formulation sequence according to master formula
- Pilot plant and manufacturing operators

High importance process factors Examples

- Film material differences
- Clear film
- WFI connection
- Agitator drive connection
- Visibility – ability to see process
- Emptying powder bag
- Emptying formulation bag
- Ergonomics

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PDA TR 66 provides comprehensive listing of factors to consider for process step

- PDA TR 66 specific considerations relevant for aseptic processing steps:
  - 4.8.1 Fluid management
  - 4.8.2 Mixing
  - 4.11 Filtration
  - 4.14 Final Filling
  - 4.15 Isolators
  - 4.16 Sampling

Product risk test approach

- Challenge: large number of possible formulations, combinations of solutions
- Extractables: Initial grouping of formulations:
  - Concentration
  - Temperature
  - Duration – plastic film contact time

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Leachables and Extractables Factors Examples, extended factor set

- Reduce analytical testing by bracketing worst case solutions (Jenke [2], BPOG [3])
- Certain complexity in defining worst case solutions
- Example factors
  - Concentration
  - Stability index
  - Temperature
  - Duration
  - Surface area
  - pH
  - Hydrophobicity
  - Ionic strength
  - Excipients

Results – process risk

- Process clearly capable (as expected)
- Major factors influencing preferred systems
  - Access
  - Handling
  - Ergonomics
  - Ability to visually check process
  - Practicalities, bag hanger, agitator mount etc.

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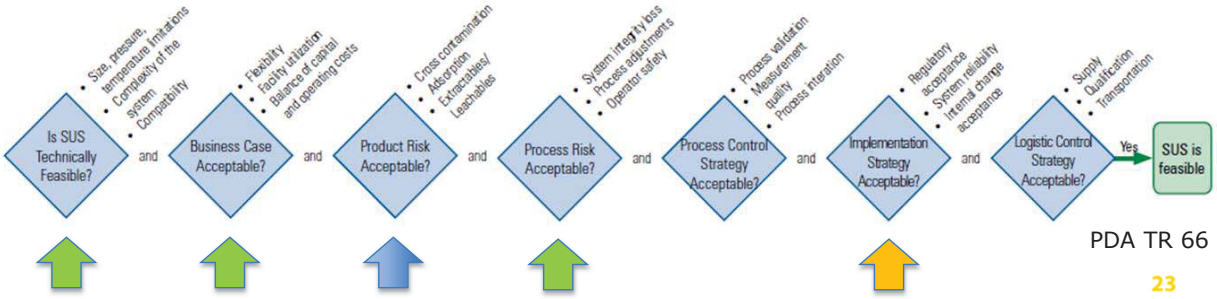
Results – additional advantage

- Interesting positive findings:
  - Shorter formulation time due to visibility of complete powder dissolution. High degree of operator acceptance.
  - Potential to minimize product loss due to bags being easy to empty fully

Results – next steps

- Productivity increase potential demonstrated
- Flexibility advantages recognized



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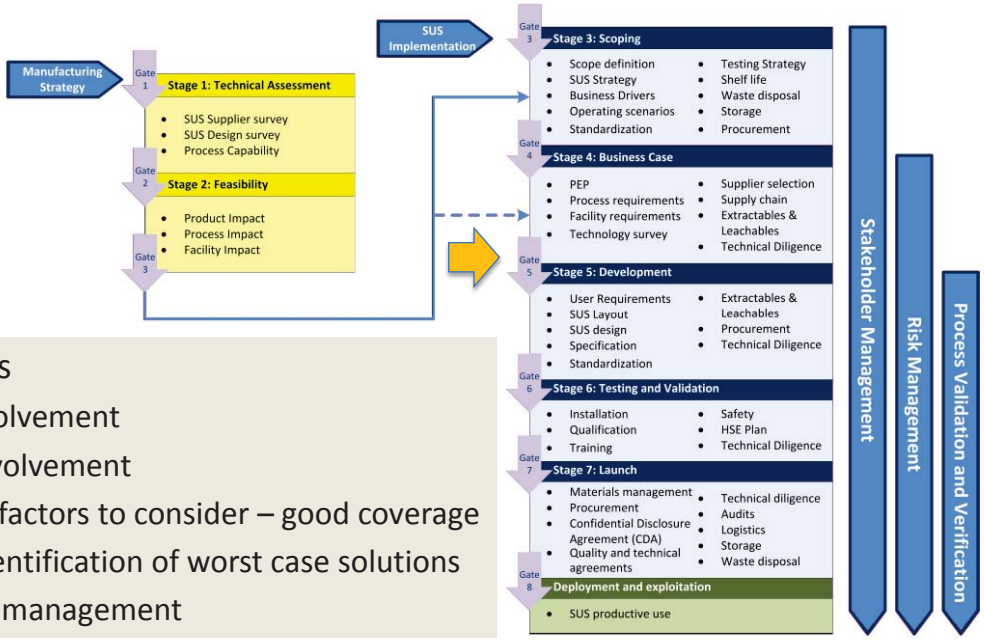
Summary: keys to success

PDA TR 66 Implementation Path Model



Keys to success

- Supplier involvement
- Operator involvement
- Process risk factors to consider – good coverage
- Stringent identification of worst case solutions
- Stakeholder management

PDA TR 66

References

[1] Technical Report no. 66: Application of Single-Use-Systems in Pharmaceutical Manufacturing, PDA, 2014

[2] Compatibility of Pharmaceutical Products and Contact Materials – Safety Considerations Associated with Extractables and Leachables, Dennis Jenke, WILEY, 2009.

[3] Standardized Extractables Testing Protocol for Single Use Systems in Biomanufacturing, ISPE Pharmaceutical Engineering, Ding, Madsen, Mahajan, O'Connor and Wong, November 2014

[4] ELSIE Extractables and Leachables Safety Information Exchange, elsiedata.org

[5] Recommendations for Extractables and Leachables Testing, Bio-Process Systems Alliance, www.bpsalliance.org, BioProcess International 5 (11), 2007, p36-49.

[6] Evaluation of Extractables and Leachables from Product-Contact Surfaces. J. Bennan et al., Biopharm Int. 15 (12), 2002, p22-34.

[7] Evaluation of safety and quality impact of extractable and leachable substances in therapeutic biologic protein products: a risk-based perspective. I. Markovic, Expert Opinion on Drug Safety, Informa Healthcare, 2007 Sep;6(5):487-91.

[8] Standard Guide for Specification, 1 Design, Verification, and 2 Application of Single-use Systems in Pharmaceutical and Biopharmaceutical Manufacturing, ASTM, 2015

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Thank you for your attention!

Questions?

Contact Details

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Question 1

- What do you see as the main barrier for increased application of single use systems?
  - 1 Product-Plastic compatibility testing
  - 2 Supply chain risk
  - 3 Volume limitations

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Question 2

- What do you see as the main realistic risk in the single use systems landscape?
  - 1 Variations in plastic film surface composition
  - 2 Supply chain disruption
  - 3 Leaks, ruptures